

In other embodiments, the method further comprises the step of making a decision on the timing and/or frequency of AMD diagnostic testing for the subject and/or on the timing and/or frequency of AMD treatment for the subject.

5 In a further embodiment, the method further comprises the step of subjecting the subject identified as having an increased risk of developing advanced AMD to AMD treatment, where the treatment may, for example, comprise administration of a medicament selected from the group consisting of anti-factor D antibodies, anti-VEGF antibodies, CRIG, and CRIG-Ig fusion.

10 In a still further embodiment, the method comprises determination of the presence or absence of risk alleles for all single nucleotide polymorphisms set forth in Table S1, and the polygenic score is calculated based on such determination.

In another embodiment, the method further comprises the step of recording the results of said determination on a computer readable medium.

In yet another embodiment, the results are communicated to the subject or the subject's physician and/or are recorded in the form of a report.

15 In another aspect, the invention concerns a report comprising the results of the methods herein.

Brief Description of the Drawings

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Figure 1: Known AMD risk genes power to predict progression.

Figure 2: Polygenic score identifies individuals a higher risk of progression to advanced AMD.

Figure 3: Polygenic score identifies individuals at higher risk of progression to advanced AMD independent of baseline clinical score.

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Table S1: List of ~~16,617~~ SNPs. CHR = chromosome; SNP = SNP ID; BP = physical position (base-pairs); A1= first (minor) allele code; F_A - allele 1 frequency in cases; F_U: allele frequency in control cases; A2 = second (major) allele code; CHISQ = CHI Square Value;

Figures 1-3. This represents a 2.6 fold increase over the unselected population, and a significant improvement in predictive power to a score composed of 7 confirmed AMD loci. Our results demonstrate that thousands of common variants can be predictive of AMD progression, and suggests that hundreds of AMD risk loci of modest individual effects contribute to the heritability of AMD.

This application includes a table entitled "Table S1." Table S1 was submitted in landscape orientation with the filing of this application. Table S1 provides a list of ~~46,617~~ SNPs. CHR = chromosome; SNP = SNP ID; BP = physical position (base-pairs); A1= first (minor) allele code; F_A - allele 1 frequency in cases; F_U: allele frequency in control cases; A2 = second (major) allele cod; CHISQ = CHI Square Value; P = p value (significance value of case/control association test); OR = Odds Ratio for the association to AMD risk. In some cases the minor allele is associated with risk (OR >1) and in some cases the major allele is associated with AMD risk (OR <1).

The results of this polygenic score analysis can be further refined and supplemented by analyzing additional genome-wide association study (GWAS) data, which are publicly available or are generated in future GWAS studies. Further refinement of the analysis can also be achieved by further analysis of the existing or future data sets, for example by comparative analysis of the choroidal neovascularization (CNV) vs. GA involving the center of the macula (CGA) data. There are also other methodologies available for determining polygenic scored, such as, for example, Support Vector Machine (SMV) algorithms.

Claims:

1. A method for assessing a human subject's risk for developing advanced age-related macular degeneration (AMD) comprising

5 (a) determining in a biological sample from said subject the presence or absence of risk alleles of common allelic variants associated with AMD at a plurality of independent loci, and

(b) calculating the polygenic score for said subject,

wherein a high polygenic score indicates a higher risk for developing advanced AMD.

10 2. The method of claim 1 wherein the allelic frequency is determined at at least 100, or at least 500, or at least 1000, or at least 2500, or at least 5,000, or at least 7,500, or at least 10,000 independent loci.

3. The method of claim 1 wherein the subject has been diagnosed with early stage AMD.

15 4. The method of claim 1 wherein the subject has been diagnosed with intermediate AMD.

5. The method of claim 1 further comprising assessing one or more aspects of the subject's personal history.

20 6. The method of claim 5 wherein said one or more aspects are selected from the group consisting of age, ethnicity, body mass index, alcohol consumption history, smoking history, exercise history, diet, family history of AMD or other age-related ocular condition, including the age of the relative at the time of their diagnosis, and a personal history of treatment of AMD.

7. The method of claim 1, wherein determining the presence or absence of risk allele is achieved by amplification of nucleic acid from said sample.

25 8. The method of claim 7, wherein amplification comprises PCR.

9. The method of claim 7, wherein primers for amplification are located on a chip.

10. The method of claim 9 wherein said primers for amplification are specific for alleles of said common genetic variants.

11. The method of claim 7 wherein the amplification comprises: (i) admixing an amplification primer or amplification primer pair with a nucleic acid template isolated from the biological sample, wherein the primer or primer pair is complementary or partially complementary to a region proximal to or including the polymorphism, and is capable of initiating nucleic acid polymerization by a polymerase on the nucleic acid template; and, b) extending the primer or primer pair in a DNA polymerization reaction comprising a polymerase and the template nucleic acid to generate the amplicon.

12. The method of claim 11, wherein the amplicon is detected by a process that includes one or more of: hybridizing the amplicon to an array, digesting the amplicon with a restriction enzyme, or real-time PCR analysis.

13. The method of claim 7, wherein the amplification comprises performing a polymerase chain reaction (PCR), reverse transcriptase PCR (RT-PCR), or ligase chain reaction (LCR) using nucleic acid isolated from the organism or biological sample as a template in the PCR, RT-PCR, or LCR.

14. The method of claim 7, further comprising cleaving amplified nucleic acid.

15. The method of claim 7, wherein said sample is derived from saliva or blood.

16. The method of claim 1, further comprising the step of making a decision on the timing and/or frequency of AMD diagnostic testing for said subject.

17. The method of claim 1, further comprising the step of making a decision on the timing and/or frequency of AMD treatment for said subject.

18. The method of claim 1, further comprising the step of subjecting the subject identified as having an increased risk of developing advanced AMD to AMD treatment.

19. The method claim 18 wherein said treatment comprises administration of a medicament selected from the group consisting of anti-factor D antibodies, anti-VEGF antibodies, CRiG, and CRiG-Ig fusion.

20. The method of claim 17 wherein said treatment comprises administration of an anti-factor D antibody.

21. The method of claim 1 wherein the presence or absence of risk alleles is determined for all single nucleotide polymorphisms set forth in Table 1.

5 22. The method of claim 21 wherein the polygenic score is calculated based on said determination.

23. The method of claim 1 further comprising the step of recording the results of said determination on a computer readable medium.

10 24. The method of claim 23 wherein said results are communicated to the subject or the subject's physician.

25. The method of claim 23 wherein said results are recorded in the form of a report.

26. A report comprising the results of the method of claim 1.

15 27. A method for assessing a human subject's risk for developing advanced age-related macular degeneration (AMD), comprising determining in a biological sample from the subject the presence or absence of risk alleles of common allelic variants associated with AMD at a plurality of independent loci.

28. The method of claim 27 wherein the risk alleles assessed exclude complement rs10737680 and rs1329424 (complement factor H); rs2285714 (complement factor I); rs429608 and rs9380272 (complement C2), rs3793917 (HTRA1); and rs2230199 (complement C3).

20 29. The method of claim 27 or claim 28 further comprising the step of determining a polygenic score for said subject.

30. The method of claim 29, wherein a high polygenic score indicates an increased likelihood that the subject will develop advanced AMD.

In other embodiments, the method further comprises the step of making a decision on the timing and/or frequency of AMD diagnostic testing for the subject and/or on the timing and/or frequency of AMD treatment for the subject.

In a further embodiment, the method further comprises the step of subjecting the subject
5 identified as having an increased risk of developing advanced AMD to AMD treatment, where the treatment may, for example, comprise administration of a medicament selected from the group consisting of anti-factor D antibodies, anti-VEGF antibodies, CRIG, and CRIG-Ig fusion.

In a still further embodiment, the method comprises determination of the presence or absence of risk alleles for all single nucleotide polymorphisms set forth in Table S1, and the
10 polygenic score is calculated based on such determination.

In another embodiment, the method further comprises the step of recording the results of said determination on a computer readable medium.

In yet another embodiment, the results are communicated to the subject or the subject's physician and/or are recorded in the form of a report.

In another aspect, the invention concerns a report comprising the results of the methods
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25 AMD independent of baseline clinical score.

Table S1: List of 10,617 SNPs. CHR = chromosome; SNP = SNP ID; BP = physical position (base-pairs); A1 = first (minor) allele code; F_A - allele 1 frequency in cases; F_U: allele frequency in control cases; A2 = second (major) allele code; CHISQ = CHI Square Value;

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5 heritability of AMD.

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The results of this polygenic score analysis can be further refined and supplemented by analyzing additional genome-wide association study (GWAS) data, which are publicly available or are generated in future GWAS studies. Further refinement of the analysis can also be achieved by further analysis of the existing or future data sets, for example by comparative analysis of the choroidal neovascularization (CNV) vs. GA involving the center of the macula (CGA) data. There are also other methodologies available for determining polygenic scored, such as, for example, Support Vector Machine (SMV) algorithms.

Claims:

1. A method for identifying a human subject diagnosed with early stage or intermediate age-related macular degeneration (AMD) as being at risk for developing advanced age-related AMD comprising
 - (a) determining in a biological sample from said subject the allelic frequency of common allelic variants associated with AMD for all single nucleotide polymorphisms set forth in Table S1, each single nucleotide polymorphism having an Odds Ratio, and
 - (b) calculating a polygenic score for said subject by multiplying the log of the Odds Ratio for each of said single nucleotide polymorphisms by the number of reference alleles carried by said human subject, and dividing the resulting sum by the number of single nucleotide polymorphisms tested, wherein a polygenic score greater than 0.0001 indicates that the subject is at risk for developing advanced AMD.
2. The method of claim 1 wherein the subject has been diagnosed with early stage AMD.
3. The method of claim 1 wherein the subject has been diagnosed with intermediate AMD.
4. The method of claim 1 further comprising assessing one or more aspects of the subject's personal history.
5. The method of claim 4 wherein said one or more aspects are selected from the group consisting of age, ethnicity, body mass index, alcohol consumption history, smoking history, exercise history, diet, family history of AMD or other age-related ocular condition, including the age of the relative at the time of their diagnosis, and a personal history of treatment of AMD.
6. The method of claim 1, wherein determining the allelic frequency is achieved by amplification of nucleic acid from said sample.
7. The method of claim 6, wherein amplification comprises PCR.
8. The method of claim 6, wherein primers for amplification are located on a chip.

9. The method of claim 8 wherein said primers for amplification are specific for alleles of said common genetic variants.
10. The method of claim 6 wherein the amplification comprises: (i) admixing an amplification primer or amplification primer pair with a nucleic acid template isolated from the biological sample, wherein the primer or primer pair is complementary or partially complementary to a region proximal to or including the polymorphism, and is capable of initiating nucleic acid polymerization by a polymerase on the nucleic acid template; and, b) extending the primer or primer pair in a DNA polymerization reaction comprising a polymerase and the template nucleic acid to generate the amplicon.
11. The method of claim 10, wherein the amplicon is detected by a process that includes one or more of: hybridizing the amplicon to an array, digesting the amplicon with a restriction enzyme, or real-time PCR analysis.
12. The method of claim 6, wherein the amplification comprises performing a polymerase chain reaction (PCR), reverse transcriptase PCR (RT-PCR), or ligase chain reaction (LCR) using nucleic acid isolated from the organism or biological sample as a template in the PCR, RT-PCR, or LCR.
13. The method of claim 6, further comprising cleaving amplified nucleic acid.
14. The method of claim 6, wherein said sample is derived from saliva or blood.
15. The method of claim 1 further comprising the step of recording the results of said determination in step (a) on a computer readable medium.
16. The method of claim 15 wherein said results are recorded in the form of a report.