

in, e.g., PCT publications WO2011/017229, WO2009/146204 and WO2009/134709. None of these references, however, disclosed or suggested correlation of the identified SNPs with how the patient's disease progresses over time or how well the patient responds to AMD therapy. In a prospective study of genetic effects on AMD progression, genetic variants such as SNPs in the complement pathway were associated with progression from intermediate drusen to large drusen and from large drusen to GA or NY. Yu et al., *Invest. Ophthalm. & Visual Sci.*, 53:1548-56 (2012). The results suggest that genes associated with AMD may be involved in transitions between distinctly different AMD stages during progression. It was not known, however, whether the identified genes are associated with rate of disease progression, e.g., within an advanced stage such as GA.

[0008] Currently, anti-VEGF (vascular endothelial growth factor) is the standard of care for treatment of most cases of the wet form of advanced AMD. There is currently no effective treatment that halts or slows the progression of GA. There is no approved treatment to prevent progression of GA, creating a significant unmet need for patients with GA. Thus, there is a need to identify efficacious therapies for GA and improved methods for understanding how to treat GA patients. Specifically, diagnostic methods useful for identifying patients at risk for increased GA progression rate and likely to benefit from anti-factor D antibody treatment would greatly benefit clinical management of these patients. This invention meets these and other needs.

[0009] All references cited herein, including patent applications and publications, are incorporated by reference in their entirety for any purpose.

Summary of the Invention

[0010] The present ~~invention~~disclosure is based in part on the novel and surprising findings collected from a clinical trial that certain polymorphisms related to genes in the complement pathway are reliable predictors for AMD patients' progression rate as well as their response to an anti-Factor D therapy. Methods of treatment, diagnosis/prognosis and predicting response to treatment as provided herein can be applied to patients suffering from age-related macular degeneration.

[0011] One embodiment of the ~~invention~~disclosure provides methods of identifying an individual who has an increased risk for progression of AMD (e.g. intermediate or advanced AMD such as wet (neovascular/exudative) AMD or geographic atrophy), the method

isolated, for example, but not to be limited to a tissue sample, a sample of saliva, a cheek swab sample, blood, or other biological fluids that contain genomic DNA. In some embodiments, the sample comprises DNA. In some embodiments, the sample comprises RNA. In some embodiments, the identity of the nucleotide at the polymorphism in a patient is determined via genotyping. In some embodiments the genotyping is performed by PCR analysis, sequence analysis or LCR analysis. In some embodiments, the patient is identified as a patient with increased risk of progression of AMD (e.g. intermediate or advanced AMD such as wet (neovascular/exudative) AMD or geographic atrophy) when at least one allele comprising a nucleotide selected from the group consisting of a G nucleotide at the SNP rs4698775 is present, a G nucleotide at the SNP rs17440077 is present, an A nucleotide at the SNP rs10737680 is present, a G nucleotide at the SNP rs1329428 is present, a G nucleotide at the SNP rs429608 is present or the G nucleotide at the SNP rs2230199 is present. The patient is identified as being at increased risk of AMD progression if the patient has one or two copies of the G allele at rs4698775 or rs17440077 associated with CFI, or equivalent alleles thereof, at rs1329428 associated with CFH, or equivalent allele thereof, or at rs429608 associated with C2/CFB, or equivalent allele thereof, or at rs2230199 associated with C3, or equivalent allele thereof or one or two copies of the A allele at rs10737680 associated with CFH, or equivalent allele thereof. The patient is identified as being at decreased risk of AMD progression if the patient does not have one or two copies of the G allele at rs4698775 or rs17440077 associated with CFI, or equivalent alleles thereof, at rs1329428 associated with CFH, or equivalent allele thereof, at rs429608 associated with C2/CFB, or equivalent allele thereof, or at rs2230199 associated with C3, or equivalent allele thereof or one or two copies of the A allele at rs10737680 associated with CFH, or equivalent allele thereof.

[0011a] In one aspect, there is provided a method of predicting progression rate of a degenerative disease in a patient having the degenerative disease, the method comprising: (a) determining the presence of at least one degenerative disease-associated polymorphism in a biological sample that has been obtained from the patient; (i) by providing a nucleic acid sample isolated from the biological sample; and (ii) detecting the genotype of the nucleic acid sample for the presence of at least one degenerative disease-associated polymorphism wherein the polymorphism is a risk allele selected from the group consisting of a CFI allele, a CFH allele, a C2 allele, a CFB allele, or a C3 allele; (b) identifying the patient as more likely to have increased rate of progression of the degenerative disease, when at least one risk allele selected from the group consisting of a CFI allele, a CFH allele, a C2 allele, a CFB allele, or a C3 allele is present.

[0012] One embodiment of the invention provides methods of predicting progression of AMD (e.g. intermediate or advanced AMD such as wet (neovascular/exudative) AMD or geographic atrophy), the method comprising determining the genotype of a patient, wherein a patient who is determined to carry a risk allele (e.g. AMD-associated polymorphism) is identified as a patient with an increased risk of progression of AMD (e.g. intermediate or advanced AMD such as wet (neovascular/exudative) AMD or geographic atrophy). In some embodiments, increased risk of progression of AMD includes progression from early AMD to intermediate AMD and intermediate to advanced AMD. In some embodiments, the risk allele is the minor allele of a selected SNP. In some embodiments, the risk allele is the major allele of a selected SNP. In

primer extension coupled with matrix-assisted laser desorption/ionization time-of-flight mass spectrometry), trityl mass tags, genotyping platforms (such as the Invader Assay®), single base primer extension (SBE) assays, PCR amplification (e.g. PCR amplification on magnetic nanoparticles (MNPs), restriction enzyme analysis of PCR products (RFLP methods), allele-specific PCR, multiple primer extension (MPEX), and isothermal smart amplification. In some embodiments, the sample is any biological sample from which genomic DNA may be isolated, for example, but not to be limited to a tissue sample, a sample of saliva, a cheek swab sample, blood, or other biological fluids that contain genomic DNA. In some embodiments, the identity of the nucleotide at the polymorphism in a patient is determined via genotyping. In some embodiments the genotyping is performed by PCR analysis, sequence analysis or LCR analysis. In some embodiments, the patient is identified as a patient with increased risk of progression of AMD (e.g. intermediate or advanced AMD such as wet (neovascular/exudative) AMD or geographic atrophy) when at least one allele comprising a nucleotide selected from the group consisting of a G nucleotide at the SNP rs4698775 is present, a G nucleotide at the SNP rs17440077 is present, an A nucleotide at the SNP rs10737680 is present, a G nucleotide at the SNP rs1329428 is present, a G nucleotide at the SNP rs429608 is present or the G nucleotide at the SNP rs2230199 is present. The patient is identified as being at increased risk of progressing to more advanced AMD if the patient has one or two copies of the G allele at rs4698775 or rs17440077 associated with CFI, or equivalent allele thereof, at rs1329428 associated with CFH, or equivalent allele thereof, at rs429608 associated with C2/CFB, or equivalent allele thereof, or at rs2230199 associated with C3, or equivalent allele thereof or one or two copies of the A allele at rs1329428 associated with CFH, or equivalent allele thereof. The patient is identified as being at decreased risk of progressing to more advanced AMD if the patient does not have one or two copies of the G allele at rs4698775 associated with CFI, or equivalent allele thereof, at rs1329428 associated with CFH, or equivalent allele thereof, at rs429608 associated with C2/CFB, or equivalent allele thereof, or at rs2230199 associated with C3, or equivalent allele thereof or one or two copies of the A allele at rs10737680 associated with CFH, or equivalent allele thereof.

[0013] The present ~~invention~~disclosure involves, at least in part, a method of treating a degenerative disease (e.g. AMD) in a patient with an anti-factor D antibody, or antigen-binding fragment thereof. In one ~~aspect~~embodiment, the ~~invention~~disclosure involves methods and compositions for treating various degenerative disorders (e.g., age-related macular degeneration) with a

complement inhibitor. In one embodiment, the degenerative disease is an ocular degenerative disease. In one embodiment, the ocular degenerative disease is age-related macular degeneration. In any of the embodiments disclosed herein, a complement inhibitor is an anti-factor D antibody, or antigen-binding fragment thereof. In some embodiments, the antibody is lampalizumab. Accordingly, one embodiment of the ~~invention~~disclosure provides methods of treating age-related macular degeneration in a patient, the method comprising administering an effective amount of an anti-factor D antibody, or antigen-binding fragment thereof, to a patient diagnosed with age-related macular degeneration, wherein the patient carries one or more risk alleles for age-related macular degeneration (e.g. AMD-associated polymorphism). In some embodiments, the risk allele is the minor allele of a selected SNP. In some embodiments, the risk allele is the major allele of a selected SNP. In some embodiments, the risk allele may be a CFI risk allele, a CFH risk allele, a C2 risk allele, a CFB risk allele and/or a C3 risk allele. In some embodiments, the risk allele is a CFI risk allele. In some embodiments, the CFI risk allele is the rs4698775:G allele, or equivalent allele thereof, or comprises a G at the selected SNP rs4698775, or comprises an alternate SNP in linkage disequilibrium to rs4698775. In some embodiments, the alternate SNP comprises a minor allele or the allele which resides on the same haplotype of the risk allele of the selected SNP rs4698775. In some embodiments, the CFI risk allele is the rs17440077 G: allele, or equivalent allele thereof, or comprises a G at the selected SNP rs17440077, or comprises an alternate SNP in linkage disequilibrium to rs17440077. In some embodiments, the alternate SNP comprises a minor allele or the allele which resides on the same haplotype of the risk allele of the selected SNP rs17440077. In some embodiments, the CFH risk allele is the rs10737680:A allele, or equivalent allele thereof, or comprises an A at the selected SNP rs10737680, or comprises an alternate SNP in linkage disequilibrium to rs10737680. In some embodiments, the alternate SNP comprises a minor allele or the allele which resides on the same haplotype of the risk allele of the selected SNP rs10737680. In some embodiments, the CFH risk allele is the rs1329428:G allele, or equivalent allele thereof, or comprises a G at the SNP rs1329428, or comprises an alternate SNP in linkage disequilibrium to rs1329428. In some embodiments, the alternate SNP comprises a minor allele or the allele which resides on the same haplotype of the risk allele of the selected SNP rs1329428. In some embodiments, the C2 risk allele is the rs429608:G allele, or equivalent allele thereof, or comprises a G at the selected SNP rs429608, or comprises an alternate SNP in linkage disequilibrium to rs429608. In some embodiments, the alternate SNP comprises a minor allele or the allele which resides

one or two copies of the A allele at rs10737680 associated with CFH, or equivalent allele thereof. In one embodiment, the study eye in the patient has a BCVA between 20/25 and 20/400. In one embodiment, the study eye in the patient has a BCVA between 20/25 and 20/100. In one embodiment, the study eye in the patient has a BCVA between 20/50 and 20/400. In one embodiment, the study eye in the patient has a BCVA between 20/50 and 20/100. In one embodiment, the study eye in the patient has a BCVA better than 20/25 or worse than 20/400. In one embodiment, the BCVA was determined using ETDRS charts. In some embodiments, the antibody or antigen-binding fragment thereof is administered intravitreally. In some embodiments, the age-related macular degeneration is dry AMD. In some embodiments, the dry AMD is advanced dry AMD. In some embodiments, the advanced dry AMD is geographic atrophy. In some embodiments, the patient has a reduced mean change in geographic atrophy (GA) area following administration of the antibody as compared to control patients that do not receive the antibody treatment. In some embodiments, the mean change in GA area is determined by measurements of GA area via standard imaging methods (e.g. fundus autofluorescence (FAF) or color fundus photography (CFP)). In some embodiments, the age-related macular degeneration is early AMD or intermediate AMD. In some embodiments, the patient with early AMD or intermediate AMD has a reduction or delay in appearance of clinical signs (e.g. may include measuring the number and size of drusen (for early and intermediate AMD) and monitoring hypo- and hyperpigmentation associated with drusen (for intermediate AMD)). In some embodiments, the methods further comprise administering a second medicament to the subject. In some embodiments, the second medicament is VEGF inhibitor.

[0013a] In another aspect, there is provided a method of identifying a patient having a degenerative disease as more likely to respond to a therapy comprising an anti-factor D antibody, or antigen-binding fragment thereof, the method comprising: (a) determining the presence of at least one degenerative disease-associated polymorphism in a biological sample that has been obtained from the patient; (i) by providing a nucleic acid sample isolated from the biological sample; and (ii) detecting the genotype of the nucleic acid sample for the presence of at least one degenerative disease-associated polymorphism, wherein the polymorphism is a risk allele selected from the group consisting of a CFI allele, a CFH allele, a C2 allele, a CFB allele, or a C3 allele; (b) identifying the patient as more likely to respond to a therapy comprising anti-factor D antibody, or an antigen-binding fragment thereof, when at least one risk allele selected from the group consisting of a CFI allele, a CFH allele, a C2 allele, a CFB allele, or a C3 allele is present. In another aspect, there is provided use of an anti-factor D antibody, or antigen-binding fragment thereof in the manufacture of a medicament for treating a patient who has been identified as a patient having a degenerative disease who is more likely to respond to a therapy comprising the anti-factor D antibody, or antigen-binding fragment thereof, according to the method described herein.

[0014] A further embodiment of the invention provides methods of identifying a degenerative disease patient (e.g. AMD patient) who may benefit from and/or respond to treatment with an anti-factor D antibody, the method comprising determining the genotype of a patient, wherein a patient who is determined to carry a risk allele is identified as a patient who may benefit from treatment with an anti-factor D antibody or antigen-binding fragment thereof. In some embodiments, the method further comprises selecting the therapy comprising an anti-factor D antibody, or antigen-binding fragment thereof. In some embodiments, the antibody is lampalizumab. In one embodiment, the degenerative disease is an ocular degenerative disease. In one embodiment, the ocular degenerative disease is age-related macular degeneration. In some embodiments, the risk allele is the minor allele of a selected SNP. In some embodiments, the risk allele is the major allele of a selected SNP. In

delay in appearance of clinical signs (e.g. may include measuring the number and size of drusen (for early and intermediate AMD) and monitoring hypo- and hyperpigmentation associated with drusen (for intermediate AMD)).

[0014a] In another aspect, there is provided a method of optimizing therapeutic efficacy of treatment of a patient having a degenerative disease with an anti-factor D antibody, or antigen binding fragment thereof, the method comprising: (a) determining the presence of at least one degenerative disease-associated polymorphism in a biological sample that has been obtained from the patient; (i) by providing a nucleic acid sample isolated from the biological sample; and (ii) detecting the genotype of the nucleic acid sample for the presence of at least one degenerative disease-associated polymorphism, wherein the polymorphism is a risk allele selected from the group consisting of a CFI allele, a CFH allele, a C2 allele, a CFB allele, or a C3 allele; (b) identifying the patient as more likely to respond to a therapy comprising anti-factor D antibody, or an antigen-binding fragment thereof, when at least one risk allele selected from the group consisting of a CFI allele, a CFH allele, a C2 allele, a CFB allele, or a C3 allele is present.

[0015] Another embodiment of the ~~invention~~disclosure provides methods of optimizing therapeutic efficacy for treatment of a degenerative disease (e.g. AMD), the method comprising determining the genotype of a patient, wherein a patient who is determined to carry a risk allele (e.g. AMD-associated polymorphism) is more likely to respond to treatment with the anti-factor D antibody, or antigen-binding fragment thereof or antigen-binding fragment thereof. In one embodiment, the degenerative disease is an ocular degenerative disease. In one embodiment, the ocular degenerative disease is age-related macular degeneration. In some embodiments, the antibody is lampalizumab. In some embodiments, the risk allele is the minor allele of a selected SNP. In some embodiments, the risk allele is the major allele of a selected SNP. In some embodiments, the risk allele may be a CFI risk allele, a CFH risk allele, a C2 risk allele, a CFB allele and/or a C3 risk allele. In some embodiments, the risk allele is a CFI risk allele. In some embodiments, the CFI risk allele is the rs4698775:G allele, or equivalent allele thereof or comprises a G at the selected SNP rs4698775, or comprises an alternate SNP in linkage disequilibrium to rs4698775. In some embodiments, the alternate SNP comprises a minor allele or the allele which resides on the same haplotype of the risk allele of the selected SNP rs4698775. In some embodiments, the CFI risk allele is the rs17440077:G allele, or equivalent allele thereof or comprises a G at the selected SNP rs17440077, or comprises an alternate SNP in linkage disequilibrium to rs17440077. In some embodiments, the alternate SNP comprises a minor allele or the allele which resides on the same haplotype of the risk allele of the selected SNP rs17440077. In some embodiments, the CFH risk allele is the rs10737680:A allele, or equivalent allele thereof, or comprises an A at the selected SNP rs10737680, or comprises an alternate SNP in linkage disequilibrium to rs10737680. In some embodiments, the alternate SNP comprises a minor allele or the allele which resides on the same haplotype of the risk allele of the selected SNP rs10737680. In some embodiments, the CFH risk allele is the rs1329428:G allele, or equivalent allele thereof, or comprises a G at the selected SNP rs1329428, or comprises an alternate SNP in linkage disequilibrium to rs1329428. In some embodiments, the alternate SNP comprises a minor allele or the allele which resides on the same haplotype of the risk allele of the selected SNP rs1329428. In some embodiments, the C2 risk allele is the rs429608:G allele, or equivalent allele thereof, or comprises a G at the selected SNP

patient has a BCVA better than 20/25 or worse than 20/400. In one embodiment, the BCVA was determined using ETDRS charts. In some embodiments, the antibody or antigen-binding fragment thereof is administered intravitreally. In some embodiments, the age-related macular degeneration is dry AMD. In some embodiments, the dry AMD is advanced dry AMD. In some embodiments, the advanced dry AMD is geographic atrophy. In some embodiments, the patient has a reduced mean change in geographic atrophy (GA) area following administration of the antibody as compared to control patients that did not receive the antibody treatment. In some embodiments, the mean change in GA area is determined by measuring GA area via standard imaging methods (e.g. fundus autofluorescence (FAF) or color fundus photography (CFP)). In some embodiments, the age-related macular degeneration is early AMD or intermediate AMD. In some embodiments, the patient with early AMD or intermediate AMD has a reduction or delay in appearance of clinical signs (e.g. may include measuring the number and size of drusen (for early and intermediate AMD) and monitoring hypo- and hyperpigmentation associated with drusen (for intermediate AMD)). In some embodiments, the methods further comprise administering a second medicament to the subject. In some embodiments, the second medicament is VEGF inhibitor.

[0015a] In another aspect, there is provided a method of predicting responsiveness of a degenerative disease patient to treatment with an anti-factor D antibody, or antigen-binding fragment thereof, the method comprising: (a) determining the presence of at least one degenerative disease-associated polymorphism in a biological sample that has been obtained from the patient; (i) by providing a nucleic acid sample isolated from the biological sample; and (ii) detecting the genotype of the nucleic acid sample for the presence of at least one degenerative disease-associated polymorphism, wherein the polymorphism is a risk allele selected from the group consisting of a CFI allele, a CFH allele, a C2 allele, a CFB allele, or a C3 allele; (b) identifying the patient as more likely to respond to a therapy comprising anti-factor D antibody, or an antigen-binding fragment thereof, when at least one risk allele selected from the group consisting of a CFI allele, a CFH allele, a C2 allele, a CFB allele, or a C3 allele is present.

[0016] Even another embodiment of the ~~invention~~disclosure provides methods of predicting responsiveness of a degenerative disease (e.g. AMD) patient to treatment with an anti-factor D antibody or antigen-binding fragment thereof, the method comprising determining the genotype of the patient, wherein a patient who is determined to carry a risk allele is identified as a patient who has an increased risk for AMD progression (e.g. GA progression) and is more likely to respond to treatment with the anti-factor D antibody or antigen-binding fragment thereof. In one embodiment, the degenerative disease is an ocular degenerative disease. In one embodiment, the ocular degenerative disease is age-related macular degeneration. In some embodiments, the antibody is lampalizumab. In some embodiments, the risk allele is the minor allele of a selected SNP. In some embodiments, the risk allele is the major allele of a selected SNP. In some embodiments, the risk allele (e.g. AMD-associated polymorphism) may be a CFI risk allele, a CFH risk allele, a C2 risk allele, a CFB risk allele and/or a C3 risk allele. In some embodiments, the risk allele is a CFI risk allele. In some embodiments, the CFI risk allele is the rs4698775:G allele, or equivalent allele thereof or comprises a G at the selected SNP rs4698775, or comprises an alternate SNP in linkage disequilibrium to rs4698775. In some embodiments, the alternate SNP comprises a

is more likely to benefit from treatment comprising an anti-factor D antibody, or antigen-binding fragment thereof when at least one allele comprising a nucleotide selected from the group consisting of a G nucleotide at the SNP rs4698775 is present, a G nucleotide at the SNP rs17440077 is present, an A nucleotide at the SNP rs10737680 is present, a G nucleotide at the SNP rs1329428 is present, a G nucleotide at the SNP rs429608 is present or the G nucleotide at the SNP rs2230199 is present. The patient is identified as being at increased risk of AMD progression if the patient has one or two copies of the G allele at rs4698775 or rs17440077 associated with CFI, or equivalent allele thereof, at rs1329428 associated with CFH, or equivalent allele thereof, at rs429608 associated with C2/CFB, or equivalent allele thereof, or at rs2230199 associated with C3, or equivalent allele thereof or one or two copies of the A allele at rs10737680 associated with CFH, or equivalent allele thereof. In one embodiment, the study eye in the patient has a BCVA between 20/25 and 20/400. In one embodiment, the study eye in the patient has a BCVA between 20/25 and 20/100. In one embodiment, the study eye in the patient has a BCVA between 20/50 and 20/400. In one embodiment, the study eye in the patient has a BCVA between 20/50 and 20/100. In one embodiment, the study eye in the patient has a BCVA better than 20/25 or worse than 20/400. In one embodiment, the BCVA was determined using ETDRS charts. In some embodiments, the antibody or antigen-binding fragment thereof is administered intravitreally. In some embodiments, the age-related macular degeneration is dry AMD. In some embodiments, the dry AMD is advanced dry AMD. In some embodiments, the advanced dry AMD is geographic atrophy. In some embodiments, the age-related macular degeneration is early AMD or intermediate AMD. In some embodiments, the patient with early AMD or intermediate AMD has a reduction or delay in appearance of clinical signs (e.g. may include measuring the number and size of drusen (for early and intermediate AMD) and monitoring hypo- and hyperpigmentation associated with drusen (for intermediate AMD)). In some embodiments, the methods further comprise administering a second medicament to the subject. In some embodiments, the second medicament is VEGF inhibitor.

[0016a] In another aspect, there is provided a method of determining the likelihood that a degenerative disease patient benefits from treatment with an anti-factor D antibody, or antigen-binding fragment thereof, the method comprising (a) determining the presence of at least one degenerative disease-associated polymorphism in a biological sample that has been obtained from the patient; (i) by providing a nucleic acid sample isolated from the biological sample; and (ii) detecting the genotype of the nucleic acid sample for the presence of at least one degenerative disease-associated polymorphism, wherein the polymorphism is a risk allele selected from the group consisting of a CFI allele, a CFH allele, a C2 allele, a CFB allele, or a C3 allele; and (b) identifying the patient as more likely to respond to a therapy comprising anti-factor D antibody, or an antigen-binding fragment thereof, when at least one risk allele selected from the group consisting of a CFI allele, a CFH allele, a C2 allele, a CFB allele, or a C3 allele is present.

[0017] Yet another embodiment of the invention provides methods for determining the likelihood that a AMD patient will benefit from treatment with an anti-factor D antibody, or antigen-binding fragment thereof, the method comprising determining genotype of the patient, wherein a patient who carries a risk allele, is identified as a patient who has an increased risk of AMD progression and is more likely to respond to treatment with an anti-factor D antibody, or antigen-binding fragment thereof. In some embodiments,

[0018] Even another embodiment of the ~~invention~~disclosure provides methods of treating degenerative disease (e.g. AMD) in a patient, the method comprising administering an effective amount of an anti-factor D antibody or antigen-binding fragment thereof to a patient diagnosed with a degenerative disease, wherein the patient has decreased progression of AMD following treatment compared to a control. In some embodiments, the antibody is lampalizumab. In one embodiment, the degenerative disease is an ocular degenerative disease. In one embodiment, the ocular degenerative disease is age-related macular degeneration. In one embodiment, the study eye in the patient has a BCVA between 20/25 and 20/400. In one embodiment, the study eye in the patient has a BCVA between 20/25 and 20/100. In one embodiment, the study eye in the patient has a BCVA between 20/50 and 20/400. In one embodiment, the study eye in the patient has a BCVA between 20/50 and 20/100. In one embodiment, the study eye in the patient has a BCVA better than 20/25 or worse than 20/400. In one embodiment, the BCVA was determined using ETDRS charts. In some embodiments, the antibody or antigen-binding fragment thereof is administered intravitreally. In some embodiments, the age-related macular degeneration is dry AMD. In some embodiments, the dry AMD is advanced dry AMD. In some embodiments, the advanced dry AMD is geographic atrophy. In some embodiments, the patient has a reduced mean change in geographic atrophy (GA) area following administration of the antibody as compared to control patients that did not receive the antibody treatment. In some embodiments, the mean change in GA area is determined by measuring the GA area by standard imaging methods (e.g. fundus autofluorescence (FAF) or color fundus photography (CFP)). In some embodiments, the age-related macular degeneration is early AMD or intermediate AMD. In some embodiments, the patient with early AMD or intermediate AMD has a reduction or delay in appearance of clinical signs (e.g. may include measuring the number and size of drusen (for early and intermediate AMD) and monitoring hypo- and hyperpigmentation associated with drusen (for intermediate AMD)). In some embodiments, the methods further comprise administering a second medicament to the subject. In some embodiments, the second medicament is VEGF inhibitor.

[0019] Even a further embodiment of the ~~invention~~disclosure provides methods of identifying an degenerative disease patient (e.g., AMD patient) who may benefit from treatment with an anti-factor D antibody, or antigen-binding fragment thereof, the method comprising determining the baseline GA area of the patient, wherein a patient who has a baseline GA area that requires clinical intervention is identified as a patient who may benefit

delivery of the anti-factor D antibody or antigen binding fragment may involve lower or higher doses than 10 mg. In some embodiments, the anti-factor D antibody, or antigen-binding fragment thereof, is administered at a dose lower than 10 mg if administered via a long-acting delivery (LAD) device. For example, the anti-factor D antibody, or antigen-binding fragment thereof is administered at a dose of 9, 8, 7, 6, 5, 4, 3, 2, 1 mg. In some embodiments, the anti-factor D antibody, or antigen-binding fragment thereof, is administered at a dose greater than 10 mg if administered intravitreally. For example, the anti-factor D antibody, or antigen-binding fragment thereof, is administered at a dose of 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 mg.

[0022] In some embodiments, the administration of the antibody is effective in one or more of the following: (1) reduction in GA area, (2) reduction of vision loss. In some embodiments, the methods described herein further comprise administering a second medicament to the patient. In some embodiments, the second medicament is a VEGF inhibitor. In some embodiments, the second medicament is a standard of care for AMD.

[0023] In another ~~aspect~~embodiment, the ~~invention~~disclosure provides a therapeutic regimen for the treatment of a patient carrying a risk allele and in need thereof comprising the administration of a factor D inhibitor. In some embodiments, the complement inhibitor is an anti-factor D antibody, or antigen-binding fragment thereof. In some embodiments, the antibody is administered at a flat dose of 5-30 mg. In some embodiments, the antibody is administered at a flat dose of 5-15 mg monthly or 10-30 mg every other month.. In some embodiments, the antibody is administered intraocularly or intravitreally. In some embodiments, the antibody is administered intravitreally at a flat dose of 5 mg or 15 mg monthly. In some embodiments, the antibody comprises a light chain comprising HVR-L1 comprising the amino acid sequence ITSTDIDDDMN (SEQ ID NO:1), HVR-L2 comprising the amino acid sequence GGNTLRP (SEQ ID NO:2), and HVR-L3 comprising the amino acid sequence LQSDSLPYT (SEQ ID NO: 3); and/or a heavy chain comprising HVR-H1 comprising the amino acid sequence GYTFTNYGMN (SEQ ID NO: 4), HVR-H2 comprising the amino acid sequence WINTYTGETTYADDFKG (SEQ ID NO:5), and HVR-H3 comprising the amino acid sequence EGGVNN (SEQ ID NO:6). In some embodiments, the antibody comprises a heavy chain variable region sequence of at least 95% sequence identity to the amino acid sequence of SEQ ID NO:7; and/or a light chain variable region sequence of at least 95% sequence identity to the amino acid sequence of SEQ ID NO:8. In some embodiments, the antibody comprises a heavy chain variable region comprising the amino acid sequence of

NO:15; and/or a light chain comprising the amino acid sequence of SEQ ID NO:16 to its respective antigenic epitope. In one embodiment, the anti-factor D antibody competitively inhibits the binding of lampalizumab having CAS registration number 1278466-20-8 to its respective antigenic epitope. In some embodiments, the anti-factor D antibody binds to the same epitope on factor D bound by another factor D antibody. In one embodiment, the anti-factor D antibody binds to the same epitope on factor D bound by the anti-factor D antibody comprising a light chain comprising HVR-L1 comprising the amino acid sequence ITSTDIDDDMN (SEQ ID NO:1), HVR-L2 comprising the amino acid sequence GGNTLRP (SEQ ID NO:2), and HVR-L3 comprising the amino acid sequence LQSDSLPYT (SEQ ID NO: 3); and/or a heavy chain comprising HVR-H1 comprising the amino acid sequence GYTFTNYGMN (SEQ ID NO: 4), HVR-H2 comprising the amino acid sequence WINTYTGETTYADDFKG (SEQ ID NO:5), and HVR-H3 comprising the amino acid sequence EGGVNN (SEQ ID NO:6). In one embodiment, the anti-factor D antibody binds to the same epitope on factor D bound by the antibody comprising a heavy chain variable region sequence of at least 95% sequence identity to the amino acid sequence of SEQ ID NO:7; and/or a light chain variable region sequence of at least 95% sequence identity to the amino acid sequence of SEQ ID NO:8. In one embodiment, the anti-factor D antibody binds to the same epitope on factor D bound by the antibody comprising a heavy chain sequence of at least 95% sequence identity to the amino acid sequence of SEQ ID NO:15; and/or a light chain sequence of at least 95% sequence identity to the amino acid sequence of SEQ ID NO:16. In one embodiment, the anti-factor D antibody binds to the same epitope on factor D bound by the antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:7; and/or a light chain variable region comprising the amino acid sequence of SEQ ID NO:8. In one embodiment, the anti-factor D antibody binds to the same epitope on factor D bound by the antibody comprising a heavy chain comprising the amino acid sequence of SEQ ID NO:15; and/or a light chain comprising the amino acid sequence of SEQ ID NO:16. In one embodiment, the anti-factor D antibody binds to the same epitope on factor D bound by lampalizumab having CAS registration number 1278466-20-8.

[0024] In another ~~aspect~~embodiment, the ~~invention~~disclosure provides a method of identifying an AMD patient who may benefit from an factor D inhibitor treatment, the method comprising determining the genotype from a sample from the patient, wherein a patient who carries the risk allele as measured by genotype assay is identified as a patient who may benefit from the factor D inhibitor treatment. In another ~~aspect~~embodiment, the ~~invention~~disclosure provides a method of predicting

responsiveness of an AMD patient to a factor D inhibitor treatment, the method comprising determining the genotype from a sample from the patient, wherein a patient who carries a risk allele is identified as a patient who is likely to respond to the factor D inhibitor treatment. In some embodiments, the genotype assay is performed using a SNP array, Taqman (Hui et al., *Current Protocol in Human Genetics*, Supp 56: 2.10.1-2.10.8 (2008)), fluorescence polarization, Sequenom or other methods for analysis of SNPs as described herein. In some embodiments, the genotype assay utilizes PCR or sequencing.

[0025] In another ~~aspect~~embodiment, the ~~invention~~disclosure provides a method of treating a degenerative disease comprising administering an anti-factor D antibody, or antigen-binding fragment thereof, comprising HVRH1, HVRH2, HVRH3, HVRL1, HVRL2, HVRL3, and HVRL3, wherein the respective HVRs have the amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6 to a patient suffering from a degenerative disease in a 10 mg dose every month. In one embodiment, the degenerative disease is an ocular degenerative disease. In one embodiment, the ocular degenerative disease is age related macular degeneration. In one embodiment, the age related macular degeneration is early, intermediate or advanced AMD. In one embodiment, the advanced AMD is geographic atrophy. In one embodiment, a second medicament is administered. In one embodiment, the second medicament is a VEGF inhibitor. In one embodiment, the VEGF inhibitor is ranibizumab. In one embodiment, the anti-factor D antibody, or antigen binding fragment thereof, is an antibody or antigen binding fragment thereof comprising a VH comprising SEQ ID NO: 7 and a VL comprising SEQ ID NO: 8. In one embodiment, the treatment results in greater than 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100% reduction of change in GA area from baseline GA area. In one embodiment, the treatment results in greater than 80% reduction of change in GA area from baseline GA area. In one embodiment, the treatment results in greater than 75% reduction of change in GA area from baseline GA area. In one embodiment, the treatment results in greater than 70% reduction of change in GA area from baseline GA area. In one embodiment, the treatment results in greater than 65% reduction of change in GA area from baseline GA area. In one embodiment, the treatment results in greater than 60% reduction of change in GA area from baseline GA area. In one embodiment, the treatment results in

greater than 55% reduction of change in GA area from baseline GA area. In one embodiment, the treatment results in greater than 50% reduction of change in GA area from baseline GA area. In one embodiment, the treatment results in greater than 45% reduction of change in GA area from baseline GA area. In one embodiment, the treatment results in greater than 40% reduction of change in GA area from baseline GA area. In one embodiment, the treatment results in greater than 35% reduction of change in GA area from baseline GA area. In one embodiment, the treatment results in greater than 30% reduction of change in GA area from baseline GA area. In one embodiment, the treatment results in greater than 25% reduction of change in GA area from baseline GA area. In one embodiment, the treatment results in greater than 20% reduction of change in GA area from baseline GA area. In one embodiment, the treatment results in greater than 15% reduction of change in GA area from baseline GA area. In one embodiment, the treatment results in greater than 10% reduction of change in GA area from baseline GA area. In one embodiment, the treatment results in greater than 5% reduction of change in GA area from baseline GA area. In one embodiment, the patient has geographic atrophy secondary to AMD. In one embodiment, the study eye in the patient has a BCVA between 20/25 and 20/400. In one embodiment, the study eye in the patient has a BCVA between 20/25 and 20/100. In one embodiment, the study eye in the patient has a BCVA between 20/50 and 20/400. In one embodiment, the study eye in the patient has a BCVA between 20/50 and 20/100. In one embodiment, the study eye in the patient has a BCVA better than 20/25 or worse than 20/400. In one embodiment, the BCVA was determined using ETDRS charts. In one embodiment, the patient has not received any previous intravitreal treatment, retinal surgery or other retinal therapeutic procedures in the study eye.

[0026] In one ~~aspect~~embodiment, the ~~invention~~disclosure provides a kit for genotyping in a biological sample from a degenerative disease patient, wherein the kit comprises oligonucleotides for polymerase chain reaction or sequencing for detection of a risk allele. In another aspect, ~~there is invention~~ provideds a kit for determining the presence of at least one degenerative disease-associated polymorphism in a biological sample, comprising reagents and instructions for detecting the genotype of the biological sample for the presence of at least one degenerative disease-associated polymorphism, wherein the polymorphism is a risk allele selected from the group consisting of a CFI allele, a CFH allele, a C2 allele, a CFB allele, or a C3 allele. In one embodiment, the biological sample is a blood sample, saliva, cheek swab, tissue sample or a sample of bodily fluids. In one embodiment, the biological sample is a nucleic acid sample.

In one embodiment, the nucleic acid sample comprises DNA. In one embodiment, the nucleic acid sample comprises RNA. In one embodiment, the nucleic acid sample is amplified. In one embodiment, the biological sample is obtained from a patient diagnosed with a degenerative disease, such as AMD, including early, intermediate and advanced AMD. In one embodiment, the advanced AMD is GA. In one embodiment, the kit further comprises a package insert for determining whether a degenerative disease patient is likely to respond to an anti-factor D antibody, or antigen binding fragment thereof. In one embodiment, the kit is used to detect the presence of a CFI risk allele, a CFH risk allele, a C2 risk allele, a CFB risk allele or a C3 risk allele. In one embodiment, the kit is used to detect the presence of one or two alleles of the G genotype at the SNP rs4698775, SNP rs17440077, SNP rs1329428, SNP rs429608 or SNP rs2230199 or two alleles of the A genotype at the SNP rs10737680. In one embodiment, the reagents of the kit comprise a set of oligonucleotides specific for detecting a polymorphism in CFI, C2, CFB, C3 or CFH allele. The oligonucleotides according to the ~~invention~~disclosure can be a forward primer and a reverse primer suitable for amplifying a region of the CFI, C2, CFB, C3 or CFH gene comprising a polymorphism in CFI, C2, CFB, C3 or CFH respectively, selected from the group consisting of the G genotype at the SNP rs4698775, SNP rs17440077, SNP rs1329428, SNP rs429608 or SNP rs2230199 or the A genotype at the SNP rs10737680. The kit can further comprises an oligonucleotide probe for detecting the polymorphism. Oligonucleotides useful as primers and probes for the ~~invention~~disclosure included those listed in Table 9 as SEQ ID NOs:17-41. In one ~~aspect~~embodiment, the reagents of the kit comprise (i) a forward primer of SEQ ID NO:17 or 18 combined with a reverse primer of SEQ ID NO:19 or 20 and a labeled probe selected from SEQ ID NOs. 21-24; (ii) a forward primer of SEQ ID NO:25 or 26 combined with a reverse primer of SEQ ID NO:27 or 28 and a labeled probe selected from SEQ ID NOs. 29-33; or (iii) a forward primer of SEQ ID NO:34 or 35 combined with a reverse primer of SEQ ID NO:36 or 37 and a labeled probe selected from SEQ ID NOs. 38-41. In one embodiment, the reagents of the kit combine primers and probes as listed in (i), (ii) and (iii) above.

[0027] In another ~~aspect~~embodiment, the ~~invention~~disclosure provides a kit for predicting whether a patient has an increased likelihood of benefiting from treatment with an anti-factor D antibody or antigen binding fragment thereof comprising a first oligonucleotide and a second oligonucleotide specific for a polymorphism in CFI, C2, CFB, C3 or CFH. In one embodiment, said first oligonucleotide and said second oligonucleotide may be used to amplify a region of the CFI, C2, CFB, C3 or CFH gene comprising a polymorphism in CFI,

C2, CFB, C3 or CFH respectively, selected from the group consisting of the G genotype at the SNP rs4698775, SNP rs17440077, SNP rs1329428, SNP rs429608 or SNP rs2230199 or the A genotype at the SNP rs10737680. In one embodiment, the anti-factor D antibody, or antigen-binding fragment thereof, comprises HVRH1, HVRH2, HVRH3, HVRL1, HVRL2, HVRL3, and HVRL3, wherein the respective HVRs have the amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6.

[0028] In one ~~aspect~~embodiment of the ~~invention~~disclosure, the anti-factor D antibody, or antigen-binding fragment thereof, comprises the variable heavy chain of SEQ ID NO: 7 and/or the variable light chain of SEQ ID NO: 8..

[0029] In one ~~aspect~~embodiment of the ~~invention~~disclosure, the polymorphism is a CFI polymorphism. In one embodiment, the CFI polymorphism is present in combination with one or more additional polymorphisms selected from the group consisting of a CFH polymorphism, a C2 polymorphism, a C3 polymorphism or a CFB polymorphism.

[0030] In one aspect, ~~there is invention~~ provideds the use of an agent that specifically binds to at least one degenerative disease-associated polymorphism wherein the polymorphism is a minor allele selected from the group consisting of a CFI risk allele, a CFH risk allele, a C2 risk allele, a CFB risk allele or a C3 risk allele for the manufacture of a diagnostic for diagnosing a degenerative disease. In one embodiment, the CFI allele is an equivalent allele thereof, the CFH allele is an equivalent allele thereof, the C2 allele is an equivalent allele thereof, the CFB allele is an equivalent allele thereof, or the C3 allele is an equivalent allele thereof. In one embodiment, the CFI allele comprises a G at the single nucleotide polymorphism (SNP) rs4698775 or rs17440077, the CFH allele comprises an A at the single nucleotide polymorphism (SNP) rs10737680 or a G at the single nucleotide polymorphism (SNP) rs1329428, the C2 allele comprises a G at the single nucleotide polymorphism (SNP) rs429608, the CFB allele comprises a G at the single nucleotide polymorphism (SNP) rs429608, and the C3 allele comprises a G at the single nucleotide polymorphism (SNP) rs2230199. In one embodiment, at least one polymorphism is detected by a technique selected from the group consisting of scanning probe and nanopore DNA sequencing, pyrosequencing, Denaturing Gradient Gel Electrophoresis (DGGE), Temporal Temperature Gradient Electrophoresis (TTGE), Zn(II)-cyclen polyacrylamide gel electrophoresis, homogeneous fluorescent PCR-based single nucleotide polymorphism analysis, phosphate-affinity polyacrylamide gel electrophoresis, high-throughput SNP genotyping

platforms, molecular beacons, 5'nuclease reaction, Taqman assay, MassArray (single base primer extension coupled with matrix-assisted laser desorption/ionization time-of-flight mass spectrometry), trityl mass tags, genotyping platforms (such as the Invader Assay®), single base primer extension (SBE) assays, PCR amplification (e.g. PCR amplification on magnetic nanoparticles (MNPs), restriction enzyme analysis of PCR products (RFLP methods), allele-specific PCR, multiple primer extension (MPEX), and isothermal smart amplification. In one embodiment, at least one polymorphism is detected by amplification of a target region containing at least one polymorphism, and hybridization with at least one sequence-specific oligonucleotide that hybridizes under stringent conditions to at least one polymorphism and detecting the hybridization. In one embodiment, the presence of one or two alleles of the G genotype at the SNP rs4698775, SNP rs17440077, SNP rs1329428, SNP rs429608 or SNP rs2230199 or one or two alleles of the A genotype at the SNP rs10737680 in the individual indicates an increased risk for degenerative disease progression. In one embodiment, a polymorphism that is in linkage disequilibrium with at least one single nucleotide polymorphism selected from the group consisting of single nucleotide polymorphism (SNP) rs4698775, rs17440077, rs10737680, rs1329428, rs429608, and rs2230199 is detected. In one embodiment, the degenerative disease is age related macular degeneration. In one embodiment, the age related macular degeneration is early, intermediate or advanced AMD. In one embodiment, the advanced AMD is geographic atrophy.

[0031] In one aspect, there is ~~is invention provided~~ an in vitro use of an agent that binds to at least one degenerative disease-associated polymorphism wherein the polymorphism is a risk allele selected from the group consisting of a CFI risk allele, a CFH risk allele, a C2 risk allele, a CFB risk allele or a C3 risk allele for identifying a patient having a degenerative disease likely to respond to a therapy comprising an anti-factor D antibody, or antigen binding fragment thereof, wherein the presence of said polymorphisms identifies that the patient is more likely to respond to the therapy. In one embodiment, the CFI allele is an equivalent allele thereof, the CFH allele is an equivalent allele thereof, the C2 allele is an equivalent allele thereof, the CFB allele is an equivalent allele thereof, or the C3 allele is an equivalent allele thereof. In one embodiment, the CFI allele comprises a G at the single nucleotide polymorphism (SNP) rs4698775 or rs17440077, the CFH allele comprises an A at the single nucleotide polymorphism (SNP) rs10737680 or a G at the single nucleotide polymorphism (SNP) rs1329428, the C2 allele comprises a G at the single nucleotide polymorphism (SNP) rs429608, the CFB allele comprises a G at the single nucleotide

polymorphism (SNP) rs429608, and the C3 allele comprises a G at the single nucleotide polymorphism (SNP) rs2230199. In one embodiment, at least one polymorphism is detected by a technique selected from the group consisting of scanning probe and nanopore DNA sequencing, pyrosequencing, Denaturing Gradient Gel Electrophoresis (DGGE), Temporal Temperature Gradient Electrophoresis (TTGE), Zn(II)-cyclen polyacrylamide gel electrophoresis, homogeneous fluorescent PCR-based single nucleotide polymorphism analysis, phosphate-affinity polyacrylamide gel electrophoresis, high-throughput SNP genotyping platforms, molecular beacons, 5' nuclease reaction, Taqman assay, MassArray (single base primer extension coupled with matrix-assisted laser desorption/ionization time-of-flight mass spectrometry), trityl mass tags, genotyping platforms (such as the Invader Assay®), single base primer extension (SBE) assays, PCR amplification (e.g. PCR amplification on magnetic nanoparticles (MNPs), restriction enzyme analysis of PCR products (RFLP methods), allele-specific PCR, multiple primer extension (MPEX), and isothermal smart amplification. In one embodiment, at least one polymorphism is detected by amplification of a target region containing at least one polymorphism, and hybridization with at least one sequence-specific oligonucleotide that hybridizes under stringent conditions to at least one polymorphism and detecting the hybridization. In one embodiment, the presence of one or two alleles of the G genotype at the SNP rs4698775, SNP rs17440077, SNP rs1329428, SNP rs429608 or SNP rs2230199 or one or two alleles of the A genotype at the SNP rs10737680 in the individual indicates an increased risk for degenerative disease progression. In one embodiment, a polymorphism that is in linkage disequilibrium with at least one single nucleotide polymorphism selected from the group consisting of single nucleotide polymorphism (SNP) rs4698775, rs17440077, rs10737680, rs1329428, rs429608, and rs2230199 is detected. In one embodiment, the degenerative disease is an ocular degenerative disease. In one embodiment, the ocular degenerative disease is age related macular degeneration. In one embodiment, the age related macular degeneration is early, intermediate or advanced AMD. In one embodiment, the advanced AMD is geographic atrophy.

[0032] In one ~~aspect~~embodiment, the ~~invention~~disclosure provides an in vitro use of a degenerative disease-associated polymorphism for selecting a patient having a degenerative disease as likely to respond to a therapy comprising an anti-factor D antibody, or an antigen-binding fragment thereof, wherein the patient is identified as more likely to respond to the therapy when the degenerative disease-associated polymorphism is detected in the sample from the patient. In one embodiment, the degenerative-disease associated polymorphism is an AMD-

polymorphism that is in linkage disequilibrium with at least one single nucleotide polymorphism selected from the group consisting of single nucleotide polymorphism (SNP) rs4698775, rs17440077, rs10737680, rs1329428, rs429608, and rs2230199 is detected. In one embodiment, the degenerative disease is an ocular degenerative disease. In one embodiment, the ocular degenerative disease is age related macular degeneration. In one embodiment, the age related macular degeneration is early, intermediate or advanced AMD. In one embodiment, the advanced AMD is geographic atrophy.

[0033] In one ~~aspect~~embodiment, the ~~invention~~disclosure provides a use of a degenerative disease-associated polymorphism for the manufacture of a diagnostic for assessing the likelihood of a response of a patient having a degenerative disease to a therapy comprising an anti-factor D antibody, or an antigen-binding fragment thereof. In one embodiment, the degenerative-disease associated polymorphism is an AMD-associated polymorphism. In one embodiment, the AMD-associated polymorphism is a risk allele selected from the group consisting of a CFI risk allele, a CFH risk allele, a C2 risk allele, a CFB risk allele or a C3 risk allele for identifying a patient having a degenerative disease likely to respond to a therapy comprising an anti-factor D antibody, or antigen binding fragment thereof, wherein the presence of said polymorphisms identifies that the patient is more likely to respond to the therapy. In one embodiment, the CFI allele is an equivalent allele thereof, the CFH allele is an equivalent allele thereof, the C2 allele is an equivalent allele thereof, the CFB allele is an equivalent allele thereof, or the C3 allele is an equivalent allele thereof. In one embodiment, the CFI allele comprises a G at the single nucleotide polymorphism (SNP) rs4698775 or rs17440077, the CFH allele comprises an A at the single nucleotide polymorphism (SNP) rs10737680 or a G at the single nucleotide polymorphism (SNP) rs1329428, the C2 allele comprises a G at the single nucleotide polymorphism (SNP) rs429608, the CFB allele comprises a G at the single nucleotide polymorphism (SNP) rs429608, and the C3 allele comprises a G at the single nucleotide polymorphism (SNP) rs2230199. In one embodiment, at least one polymorphism is detected by a technique selected from the group consisting of scanning probe and nanopore DNA sequencing, pyrosequencing, Denaturing Gradient Gel Electrophoresis (DGGE), Temporal Temperature Gradient Electrophoresis (TTGE), Zn(II)-cyclen polyacrylamide gel electrophoresis, homogeneous fluorescent PCR-based single nucleotide polymorphism analysis, phosphate-affinity polyacrylamide gel electrophoresis, high-throughput SNP genotyping platforms, molecular beacons, 5' nuclease reaction, Taqman assay, MassArray (single base primer extension coupled with matrix-assisted laser desorption/ionization time-of-flight mass

spectrometry), trityl mass tags, genotyping platforms (such as the Invader Assay®), single base primer extension (SBE) assays, PCR amplification (e.g. PCR amplification on magnetic nanoparticles (MNPs), restriction enzyme analysis of PCR products (RFLP methods), allele-specific PCR, multiple primer extension (MPEX), and isothermal smart amplification. In one embodiment, at least one polymorphism is detected by amplification of a target region containing at least one polymorphism, and hybridization with at least one sequence-specific oligonucleotide that hybridizes under stringent conditions to at least one polymorphism and detecting the hybridization. In one embodiment, the presence of one or two alleles of the G genotype at the SNP rs4698775, SNP rs17440077, SNP rs1329428, SNP rs429608 or SNP rs2230199 or one or two alleles of the A genotype at the SNP rs10737680 in the individual indicates an increased risk for degenerative disease progression. In one embodiment, a polymorphism that is in linkage disequilibrium with at least one single nucleotide polymorphism selected from the group consisting of single nucleotide polymorphism (SNP) rs4698775, rs17440077, rs10737680, rs1329428, rs429608, and rs2230199 is detected. In one embodiment, the degenerative disease is an ocular degenerative disease. In one embodiment, the ocular degenerative disease is age related macular degeneration. In one embodiment, the age related macular degeneration is early, intermediate or advanced AMD. In one embodiment, the advanced AMD is geographic atrophy.

[0034] In one ~~aspect~~embodiment, the ~~invention~~disclosure provides an oligonucleotide for detecting polymorphisms at one or more nucleotide positions in complement-associated loci. In one embodiment, the complement-associated loci are selected from CFH, CFI, C3, C2 and CFB risk loci. In one embodiment, the nucleotide position is selected from the group consisting of nucleotide positions associated with rs4698775, rs17440077, rs10737680, rs1329428, rs429608 and rs2230199. In one embodiment the oligonucleotide is at least 90% identical to and having the 3'terminal nucleotide of one or more of the sequences selected from the group consisting of SEQ ID NOs:17-41. The oligonucleotides might comprise 3 or fewer mismatches with one of said sequences, excluding the 3'-terminal nucleotide and/or at least one mismatch among the penultimate 5 nucleotides at the 3'-terminus. The oligonucleotides might further comprise at least one modified nucleotide among the terminal 5 nucleotides at the 3'-terminus. In some embodiments, the oligonucleotide is suitable for detecting one or more of the alleles of rs4698775, rs17440077, rs10737680, rs1329428, rs429608, and rs2230199.

[0035] In one ~~aspect~~embodiment, the ~~invention~~disclosure is a diagnostic method of detecting SNPs in the CFH, CFI, C3, C2 or CFB risk loci. In one embodiment, the SNP is selected from rs4698775, rs17440077, rs10737680, rs1329428, rs429608, and rs2230199. In one embodiment, the SNP is detected using oligonucleotides selected from SEQ ID NOs:17-41 or variations at least 90% identical thereto and having the 3'-terminal nucleotide of said oligonucleotide. In one embodiment, the method comprises contacting a biological sample containing nucleic acids with one or more of the oligonucleotides in the presence of the corresponding downstream primer and detection probe. Advantageously, detection of several SNPs can be performed in a single reaction. In some embodiments, several closely positioned polymorphisms can be detected in a single reaction containing two or more allele-specific oligonucleotides, e.g. selected from sequences listed in Table 9 that can be combined in one reaction mixture with a single downstream primer and optionally a single detection probe. In a further embodiment, the method comprises contacting a test sample containing nucleic acids with one or more of the oligonucleotides as SNP-specific probes in the presence of the corresponding forward and reverse primers (i.e. primers capable of hybridizing to the opposite strands of the target DNA nucleic acids so as to enable exponential amplification), nucleoside triphosphates and a nucleic acid polymerase, such that the one or more allele-specific primers is efficiently extended only when a mutation is present in the sample; and detecting the presence or absence of a mutation by directly or indirectly detecting the presence or absence of the primer extension.

[0036] In a particular embodiment the presence of the primer extension is detected with a probe. The probe may be labeled with a radioactive, or a chromophore (fluorophore) label, e.g. a label incorporating FAM, JA270, CY5 family dyes, or HEX dyes. As one example of detection using a fluorescently labeled probe, the mutation may be detected by real-time polymerase chain reaction (rt-PCR), where hybridization of the probe results in enzymatic digestion of the probe and detection of the resulting fluorescence (TaqMan™ probe method, Holland *et al.* (1991) P.N.A.S. USA 88:7276-7280). Alternatively, the presence of the extension product and the amplification product may be detected by gel electrophoresis followed by staining or by blotting and hybridization as described e.g., in Sambrook, J. and Russell, D.W. (2001) *Molecular Cloning*, 3rd ed. CSHL Press, Chapters 5 and 9.

[0037] In some embodiments, the factor D inhibitor as described herein and in the uses described herein is an anti-factor D antibody. The antibody specifically binds Factor D.

[0038] In another ~~aspect~~embodiment, the ~~invention~~disclosure provides an article of manufacture comprising an IVT administration device, which delivers to a patient a flat dose of an anti-factor D antibody, or antigen-binding fragment thereof, wherein the flat dose is in the microgram to milligram range. In some embodiments, the flat dose is 10 mg monthly or 10 mg every other month. In some embodiments, the concentration of the antibody in the device is about 10 mg. In another ~~aspect~~embodiment, the ~~invention~~disclosure provides an article of manufacture comprising an anti-factor D antibody, or antigen-binding fragment thereof in a concentration of 10 mg. In some embodiments, the antibody comprises a light chain comprising HVR-L1 comprising the amino acid sequence ITSTDIDDDMN (SEQ ID NO:1), HVR-L2 comprising the amino acid sequence GGNTLRP (SEQ ID NO:2), and HVR-L3 comprising the amino acid sequence LQSDSLPYT (SEQ ID NO: 3); and/or a heavy chain comprising HVR-H1 comprising the amino acid sequence GYTFTNYGMN (SEQ ID NO: 4), HVR-H2 comprising the amino acid sequence WINTYTGETTYADDFKG (SEQ ID NO:5), and HVR-H3 comprising the amino acid sequence EGGVNN (SEQ ID NO:6). In some embodiments, the antibody comprises a heavy chain variable region sequence of at least 95% sequence identity to the amino acid sequence of SEQ ID NO:7; and/or a light chain variable region sequence of at least 95% sequence identity to the amino acid sequence of SEQ ID NO:8. In some embodiments, the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:7; and/or a light chain variable region comprising the amino acid sequence of SEQ ID NO:8. In some embodiments, the antibody is lampalizumab having CAS registration number 1278466-20-8.

[0039] In another ~~aspect~~embodiment, the ~~invention~~disclosure provides a kit for identifying a degenerative disease patient who may benefit for a factor D inhibitor treatment, comprising a vial for collecting a blood sample from a degenerative disease patient and instructions for determining whether the degenerative disease patient carries a risk allele. In some embodiments, the presence of at least one SNP from the group consisting of complement factor I (CFI), complement factor H (CFH), complement factor B (CFB), complement component 3 (C3) and complement component 2 (C2) is used to determine whether the degenerative disease patient carries the risk allele. In one embodiment, the degenerative disease is an ocular degenerative disease. In some embodiments, the ocular degenerative disease is AMD. In some embodiments, the factor D inhibitor is an anti-factor D antibody, or antigen-binding fragment thereof.

[0040] In another ~~aspect~~embodiment, the ~~invention~~disclosure provides a stable lyophilized composition, which, after reconstitution with sterile water for injection, comprises an anti-factor D antibody, or antigen-binding fragment thereof in an amount of about 80 to about 120 mg/mL, sodium chloride in an amount of about 8 to about 40 mM, sucrose in the amount of about 80 mM to about 240 mM, L-histidine in an amount of about 10 to about 60 mM, polysorbate 20 in an amount of about 0.01 to about 0.08% w/v, wherein the composition has a pH from about 5.0 to about 6.0.

[0041] It is to be understood that one, some, or all of the properties of the various embodiments described herein may be combined to form other embodiments of the present ~~invention~~disclosure. These and other aspects of the invention will become apparent to one of skill in the art. These and other embodiments of the ~~invention~~disclosure are further described in the detailed description that follows.

Brief Description of the Drawings

[0042] Figure 1 depicts a diagram of the study design for the MAHALO trial described in Example 1 below.

[0043] Figure 2A is a table summarizing baseline characteristics for all efficacy-evaluable patients (n = 123) from the phase II component of the study described in Example 1. “Efficacy-evaluable patients” as used herein are defined as all randomized patients who receive at least one injection of treatment and had at least one post-baseline GA area measurement. Figure 2B is a table summarizing baseline characteristics of assayed patients based on CFI status, with risk allele carriers defined as individuals heterozygous or risk-allele homozygous at the SNP being tested. VA = visual acuity. GA = geographic atrophy. DA = disc area (1 DA = 2.54 mm²).

[0044] Figures 3A and 3B show the preliminary efficacy results after the primary database lock for the MAHALO phase II study with an all-comers population; the study met its primary endpoint of mean change from baseline in GA area at 18 months as measured by fundus autofluorescence (FAF) and met its secondary endpoint of mean change from baseline in GA area at 18 months as assessed by color fundus photography (CFP) in the lampalizumab monthly group. A positive treatment effect in slowing the progression of GA area growth was observed in the monthly group beginning at 6 months and extending through 18 months with primary (FAF) and secondary (CFP) imaging endpoints. Figure 3A shows that on the basis of the unadjusted means with the LOCF data, the lampalizumab monthly arm had a

WHAT IS CLAIMED IS:

1. A method of predicting progression rate of a degenerative disease in a patient having the degenerative disease, the method comprising:

(a) determining the presence of at least one degenerative disease-associated polymorphism in a biological sample that has been obtained from the patient;

(i) by providing a nucleic acid sample isolated from the biological sample; and

(ii) detecting the genotype of the nucleic acid sample for the presence of at least one degenerative disease-associated polymorphism wherein the polymorphism is a risk allele selected from the group consisting of a CFI allele, a CFH allele, a C2 allele, a CFB allele, or a C3 allele;

(b) identifying the patient as more likely to have increased rate of progression of the degenerative disease, when at least one risk allele selected from the group consisting of a CFI allele, a CFH allele, a C2 allele, a CFB allele, or a C3 allele is present.

2. The method of claim 1 wherein the CFI allele is an equivalent allele thereof, the CFH allele is an equivalent allele thereof, the C2 allele is an equivalent allele thereof, the CFB allele is an equivalent allele thereof, or the C3 allele is an equivalent allele thereof.

3. The method of claim 1 wherein the CFI allele comprises a G at the single nucleotide polymorphism (SNP) rs4698775 or rs17440077, the CFH allele comprises an A at the single nucleotide polymorphism (SNP) rs10737680 or a G at the single nucleotide polymorphism (SNP) rs1329428, the C2 allele comprises a G at the single nucleotide polymorphism (SNP) rs429608, the CFB allele comprises a G at the single nucleotide polymorphism (SNP) rs429608, and the C3 allele comprises a G at the single nucleotide polymorphism (SNP) rs2230199.

4. The method of claim 1 wherein the biological sample is a blood sample, saliva, cheek swab, tissue sample or a sample of a bodily fluid.

5. The method of claim 1 wherein the nucleic acid sample comprises DNA.

6. The method of claim 1 wherein the nucleic acid sample comprises RNA.

7. The method of claim 1 wherein the nucleic acid sample is amplified.

8. The method of claim 7 wherein the nucleic acid sample is amplified by a polymerase chain reaction.

17. The method of claim 16 wherein the advanced AMD is geographic atrophy (GA).
18. The method of claim 1 wherein the genotype is detected by PCR using a set of oligonucleotides selected from SEQ ID NOs: 17-41 for respective alleles according to Table 9, and wherein the patient is identified as more likely to have increased progression rate when the risk allele G at SNP rs4698775 for CFI allele is present along with at least one risk allele G at either SNP rs1329428 for CFH allele or SNP rs429608 for C2/CFB allele.
19. The method of claim 18, wherein the set of oligonucleotides include a forward primer selected from the group consisting of SEQ ID NOs. 17, 18, 25, 26, 34 and 35; a reverse primer selected from the group consisting of SEQ ID NOs. 19, 20, 27, 28, 36 and 37 and a labeled probe selected from the group consisting of SEQ ID NOs. 21-24, 29-33, and 38-41, according to Table 9.
20. The method of claim 19, wherein the genotype at rs4698775 (CFI) is detected using a forward primer of SEQ ID NO:17 or 18 combined with a reverse primer of SEQ ID NO:19 or 20 and a labeled probe selected from SEQ ID NOs. 21-24; the genotype at rs429608 (C2) is detected using a forward primer of SEQ ID NO:25 or 26 combined with a reverse primer of SEQ ID NO:27 or 28 and a labeled probe selected from SEQ ID NOs. 29-33; and the genotype at rs1329428 (CFH) is detected using a forward primer of SEQ ID NO:34 or 35 combined with a reverse primer of SEQ ID NO:36 or 37 and a labeled probe selected from SEQ ID NOs. 38-41.
21. A method of identifying a patient having a degenerative disease as more likely to respond to a therapy comprising an anti-factor D antibody, or antigen-binding fragment thereof, the method comprising:
 - (a) determining the presence of at least one degenerative disease-associated polymorphism in a biological sample that has been obtained from the patient;
 - (i) by providing a nucleic acid sample isolated from the biological sample; and
 - (ii) detecting the genotype of the nucleic acid sample for the presence of at least one degenerative disease-associated polymorphism, wherein the polymorphism is a risk allele selected from the group consisting of a CFI allele, a CFH allele, a C2 allele, a CFB allele, or a C3 allele;
 - (b) identifying the patient as more likely to respond to a therapy comprising anti-factor D antibody, or an antigen-binding fragment thereof, when at least one risk allele

49. A method of optimizing therapeutic efficacy of treatment of a patient having a degenerative disease with an anti-factor D antibody, or antigen binding fragment thereof, the method comprising:

- (a) determining the presence of at least one degenerative disease-associated polymorphism in a biological sample that has been obtained from the patient;
 - (i) by providing a nucleic acid sample isolated from the biological sample; and
 - (ii) detecting the genotype of the nucleic acid sample for the presence of at least one degenerative disease-associated polymorphism, wherein the polymorphism is a risk allele selected from the group consisting of a CFI allele, a CFH allele, a C2 allele, a CFB allele, or a C3 allele;
- (b) identifying the patient as more likely to respond to a therapy comprising anti-factor D antibody, or an antigen-binding fragment thereof, when at least one risk allele selected from the group consisting of a CFI allele, a CFH allele, a C2 allele, a CFB allele, or a C3 allele is present.

50. A method of predicting responsiveness of a degenerative disease patient to treatment with an anti-factor D antibody, or antigen-binding fragment thereof, the method comprising:

- (a) determining the presence of at least one degenerative disease-associated polymorphism in a biological sample that has been obtained from the patient;
 - (i) by providing a nucleic acid sample isolated from the biological sample; and
 - (ii) detecting the genotype of the nucleic acid sample for the presence of at least one degenerative disease-associated polymorphism, wherein the polymorphism is a risk allele selected from the group consisting of a CFI allele, a CFH allele, a C2 allele, a CFB allele, or a C3 allele;
- (b) identifying the patient as more likely to respond to a therapy comprising anti-factor D antibody, or an antigen-binding fragment thereof, when at least one risk allele selected from the group consisting of a CFI allele, a CFH allele, a C2 allele, a CFB allele, or a C3 allele is present.

51. A method of determining the likelihood that a degenerative disease patient benefits from treatment with an anti-factor D antibody, or antigen-binding fragment thereof, the method comprising

- (a) determining the presence of at least one degenerative disease-associated polymorphism in a biological sample that has been obtained from the patient;
- (i) by providing a nucleic acid sample isolated from the biological sample; and
- (ii) detecting the genotype of the nucleic acid sample for the presence of at least one degenerative disease-associated polymorphism, wherein the polymorphism is a risk allele selected from the group consisting of a CFI allele, a CFH allele, a C2 allele, a CFB allele, or a C3 allele; and
- (b) identifying the patient as more likely to respond to a therapy comprising anti-factor D antibody, or an antigen-binding fragment thereof, when at least one risk allele selected from the group consisting of a CFI allele, a CFH allele, a C2 allele, a CFB allele, or a C3 allele is present.

52. A kit for determining the presence of at least one degenerative disease-associated polymorphism in a biological sample, comprising reagents and instructions for detecting the genotype of the biological sample for the presence of at least one degenerative disease-associated polymorphism, wherein the polymorphism is a risk allele selected from the group consisting of a CFI allele, a CFH allele, a C2 allele, a CFB allele, or a C3 allele.

53. The kit of claim 52 wherein the biological sample is a blood sample, saliva, cheek swab, tissue sample or a sample of bodily fluids.

54. The kit of claim 52 wherein the biological sample is one that has been obtained from a patient diagnosed with a degenerative disease.

55. The kit of claim 52 wherein the degenerative disease is age related macular degeneration (AMD).

56. The kit of claim 55 wherein the AMD is early, intermediate or advanced AMD.

57. The kit of claim 56 wherein the advanced AMD is geographic atrophy (GA).

58. A kit according to claim 52, wherein the kit further comprises a package insert for determining whether a degenerative disease patient is likely to respond to an anti-factor D antibody, or antigen binding fragment thereof.

59. A kit according to claim 52 wherein the kit is used to detect the presence of a CFI risk allele, a CFH risk allele, a C2 risk allele, a CFB risk allele or a C3 risk allele.

nanoparticles (MNPs), restriction enzyme analysis of PCR products (RFLP methods), allele-specific PCR, multiple primer extension (MPEX), and isothermal smart amplification.

81. The use of claim 77 wherein at least one polymorphism is detected by amplification of a target region containing at least one polymorphism, and hybridization with at least one sequence-specific oligonucleotide that hybridizes under stringent conditions to at least one polymorphism and detecting the hybridization.

82. The use of claim 77 wherein the presence of one or two alleles of the G genotype at the SNP rs4698775, SNP rs17440077, SNP rs1329428, SNP rs429608 or SNP rs2230199 or one or two alleles of the A genotype at the SNP rs10737680 in the individual indicates an increased risk for degenerative disease progression.

83. The use of claim 79 wherein a polymorphism that is in linkage disequilibrium with at least one single nucleotide polymorphism selected from the group consisting of single nucleotide polymorphism (SNP) rs4698775, rs17440077, rs10737680, rs1329428, rs429608, and rs2230199 is detected.

84. The use of claim 77 wherein the degenerative disease is age related macular degeneration.

85. The use of claim 84 wherein the age related macular degeneration is early, intermediate or advanced AMD.

86. The use of claim 85 wherein the advanced AMD is geographic atrophy.

87. Use of an anti-factor D antibody, or antigen-binding fragment thereof in the manufacture of a medicament for treating a patient who has been identified as a patient having a degenerative disease who is more likely to respond to a therapy comprising the anti-factor D antibody, or antigen-binding fragment thereof, according to the method of claim 21.

88. The use of claim 87, wherein the anti-factor D antibody, or antigen-binding fragment thereof, comprises HVRH1, HVRH2, HVRH3, HVRL1, HVRL2, HVRL3, and HVRL3, wherein the respective HVRs have the amino acid sequence of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6.

89. The use of claim 87, wherein the anti-factor D antibody, or antigen-binding fragment thereof, comprises the variable heavy chain of SEQ ID NO:7 and/or the variable light chain of SEQ ID NO:8.

90. The use of claim 87, wherein the anti-factor D antibody, or fragment thereof is lampalizumab.