Clinical Evaluation of 3 Families With Basal Laminar Drusen Caused by Novel Mutations in the Complement Factor H Gene

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Objectives: To identify novel complement factor H (CFH) gene mutations and to specify the characteristic features in patients with basal laminar drusen (BLD), a clinical subtype of age-related macular degeneration.

Methods: Twenty-one probands with BLD were included in this study. The ophthalmic examination included nonstereoscopic 30° color fundus photography, fluorescein angiography, and high-resolution spectral-domain optical coherence tomography. Renal function was tested by measurement of serum creatinine and urea nitrogen levels. Venous blood samples were drawn for genomic DNA, and all coding exons and splice junctions of the CFH gene were analyzed by direct sequencing.

Results: In 3 families, we identified novel heterozygous mutations in the CFH gene: p.Ile184fsX, p.Lys204fsX, and c.1697-17_−8del. Ten of 13 mutation carriers displayed the BLD phenotype with a wide variety in clinical presentation, ranging from limited macular drusen to extensive drusen in the posterior pole as well as the peripheral retina. Two patients with BLD developed end-stage kidney disease as a result of membranoproliferative glomerulonephritis type II.

Conclusions: The early-onset BLD phenotype can be caused by heterozygous mutations in the CFH gene. Because some patients with BLD are at risk to develop membranoproliferative glomerulonephritis type II, we recommend that patients with extensive BLD undergo screening for renal dysfunction.

Clinical Relevance: Elucidation of the clinical BLD phenotype will facilitate identification of individuals predisposed to developing disease-related comorbidity, such as membranoproliferative glomerulonephritis type II. Moreover, with upcoming treatment modalities targeting specific components of the complement system, early identification of patients with BLD and detection of the genetic defect become increasingly important.
ated proteolytic inactivation of C3b. By this mechanism, CFH is essential to maintain complement homeostasis in plasma and to restrict complement activation on complement activating self-surfaces such as the retinal pigment epithelium.

Age-related macular degeneration is characterized by multiple heterogeneous subtypes, with drusen as the hallmark lesions and usually the first clinical finding. Basal laminar drusen (BLD), also termed cuticular drusen or early adult onset, grouped drusen, is one of the subtypes in the AMD spectrum. The BLD phenotype shows characteristic innumerable, small, subretinal, raised yellow drusen that are hyperfluorescent on fluorescein angiography, resulting in a typical “stars-in-the-sky” appearance. The BLD phenotype is also associated with the p.Tyr402His variant in the CFH gene, with a risk allele frequency up to 70% vs 55% in “typical” AMD-affected individuals. Boon and colleagues found an association of compound heterozygous variants in the CFH gene with BLD. Specific mutations and variants in the CFH gene are associated with a broad range of phenotypes, from early-onset renal diseases with high mortality rates to disorders limited to the eye, such as AMD. Some patients have concurrent renal and retinal abnormalities. It has been postulated that the type, onset, and severity of renal and/or retinal abnormalities show a considerable degree of genotype-phenotype correlation.

The purposes of this study were to identify novel CFH gene mutations and to specify the clinical characteristics in patients with BLD.

METHODS

In this study, we included 21 probands diagnosed as having AMD who were noted on initial examination to have BLD on fluorescein angiography and 192 ethnically matched control subjects of similar age who showed no signs of maculopathy. Informed consent was obtained from all subjects after explanation of the nature and possible consequences of the study. We conducted the study in accordance with the tenets of the Declaration of Helsinki, and it was approved by the Committee on Research Involving Human Subjects at the Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands.

OPHTHALMIC EXAMINATION

Ophthalmic examination of the subjects included Early Treatment Diabetic Retinopathy Study visual acuity and slitlamp biomicroscopy after pupil dilatation. Digital nonstereoscopic 30° color fundus photographs were taken with a digital fundus camera (Topcon TRC 30IX; Topcon Corporation). To confirm the diagnosis of BLD, we performed fluorescein angiography and high-resolution Fourier-domain optical coherence tomography using the combined confocal scanning laser ophthalmoscope/Fourier-domain optical coherence tomography device (Spectralis; Heidelberg Engineering). In the early stages, the diagnosis was based on fluorescein angiographic confirmation of innumerable small drusen in the macula and/or periretinal retina, giving a symmetrically distributed pattern of innumerable, scattered, uniformly sized, small (25- to 75-μm) hyperfluorescent lesions in both eyes. The occurrence of confluent (soft) drusen in the macular region and the subsequent development of a drusenoid pigment epithelial detachment are considered characteristic for the late stages of this disease.

RESULTS

In 3 of the 21 probands, we identified novel heterozygous mutations in the CFH gene: 2 frameshift mutations in exon 5 and 1 splice-site mutation in the splice-acceptor site of exon 12 (Figure 1). None of these CFH mutations were identified in 192 control subjects who had no signs of maculopathy, and no nonsense, frameshift, or splice-site mutations were identified in 369 ethnically matched controls from our in-house exome database.

The probands who carried a mutation in the CFH gene could not be distinguished clinically from the probands who did not carry a CFH mutation (Table 1). Of the 20 additional family members who underwent screening for the novel CFH gene mutations, 10 were shown to carry the same mutation as the proband, of whom 7 proved to be affected by BLD (Figure 2 and Table 2). However, only the probands of the 3 families noticed visual loss before the diagnosis of BLD was established.

Of all the patients carrying a mutation in CFH, 5 (in families A and B) were compound heterozygous for the novel CFH mutation together with the AMD risk allele p.Tyr402His in the CFH gene. The other 8 patients (in families A, B, and C) did not carry the p.Tyr402His risk allele or carried it heterozygously on the same allele as the mutation. An overview of the clinical and genetic characteristics of the 3 families is given in Table 2.

FAMILY A

In family A, we identified the heterozygous c.550delA; p.Ile184fsX frameshift mutation in exon 5. This muta-
tion occurs in the third short consensus repeat of the CFH protein.

The proband of family A (A-II:3) first noticed metamorphopsia and a decrease in visual acuity in both eyes at age 56 years. Ophthalmoscopy revealed extensive small and large confluent drusen in the posterior pole with a drusenoid pigment epithelial detachment in the macula of both eyes (Figure 3B and H). Among the affected siblings of the proband, patient A-II:1 (aged 64 years) showed hard drusen in the midperipheral retina, mostly located temporal to the fovea, whereas patient A-II:5 (aged 61 years) had dense, macular, small and soft confluent drusen (Figure 3A and C). Small hard drusen were seen in the peripheral retina of patient A-III:1 (aged 31 years) and A-III:2 (aged 27 years), with increasing numbers of these peripheral drusen with increasing age (Figure 3D, E, and G). Additional macular hard drusen were observed only in the oldest mutation carrier of the third generation (A-III:1) but to a lesser extent compared with his father (A-II:1). Patient A-III:4, the youngest mutation carrier in this family (aged 18 years) had some soft drusen in the peripheral retina but no hard drusen as were found in other family members carrying the c.550delA mutation (Figure 3F).

FAMILY B

In family B, we identified the heterozygous c.607-610dupCCAA; p.Lys204fsX frameshift mutation in exon 5. As was the case for the c.550delA mutation in family A, this mutation also occurs in the region of the third short consensus repeat in the CFH protein.

Patient B-II:1, the proband of family B, first noticed visual loss, associated metamorphopsia, and small central scotomas in both eyes at age 47 years. The proband and her affected siblings (B-II:4 and B-II:6) showed an equivalent BLD phenotype of innumerable macular hard and soft drusen, with small hard drusen extending toward the peripheral retina that were symmetrical in both fundi (Figure 4). The hard drusen in the peripheral retina had only a thin hyperpigmented border. Three years after the initial visual complaints, the proband reported increasing metamorphopsia and a rapid decrease in visual acuity from 20/20 to 20/67 of the left eye due to classic CNV in the left eye. This neovascularization was treated successfully during a period of 3 months with 3 intravitreal injections of bevacizumab, 0.05 mL (25 mg/mL), at an interval of 4 weeks, resulting in increased visual acuity to 20/24 in that eye for 2 years as of the last examination.

In addition to extensive BLD, patient B-II:1 was diagnosed as having end-stage membranoproliferative glomerulonephritis (MPGN) type II, also known as dense deposit disease, at age 48 years. She is currently being treated with peritoneal dialysis and is a candidate for a renal transplant in the near future. The other mutation-carrying family members also underwent screening for renal dysfunction but showed no abnormalities.

FAMILY C

In family C, we identified 3 individuals with the heterozygous CFH gene mutation (c.1697-17_-8del) in the splice-acceptor site. This mutation is predicted to abolish the splice-acceptor site of exon 12 of the CFH gene given that the splice prediction score is reduced from 0.62 to 0 (as calculated by the splice-site prediction program NNSPLICE, version 0.9; http://www.fruitfly.org/seq_tools/splice.html).

Only patient C-II:4 was affected with BLD. He reported a rapid decrease in visual acuity from 20/20 to 20/35 and metamorphopsia of the right eye at age 55 years. Both fundi showed a pigment epithelial detachment and pigmentary changes in the macular area, together with numerous small hard drusen in the midperipheral retina, mostly located temporal to the fovea. The right eye also showed a large area of paravascular subretinal hemorrhage (Figure 5A and B). In both eyes, fluorescein angiography revealed more dense and well-circumscribed hyperfluorescent BLD than were seen during direct oph-
Thalamscopy. In addition, the angiography revealed parafoveal occult CNV in the right eye. This patient was treated successfully with 4 intravitreal injections of bevacizumab, 0.05 mL (25 mg/mL), during a period of 6 months, resulting in an increased and stabilized visual acuity of 20/20 without metamorphopsia for 3 years to date.

Table 1. Clinical and Genetic Characteristics of the 21 Evaluated Probands

<table>
<thead>
<tr>
<th>Patient Code/Age at Onset, y/Sex</th>
<th>Age, y</th>
<th>Visual Acuity OD</th>
<th>OS</th>
<th>Retinal Phenotype</th>
<th>CFH Mutation</th>
<th>CFH p.Tyr402His, Allele 1/Allele 2a</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-II:3/56/M</td>
<td>62</td>
<td>20/25</td>
<td>20/33</td>
<td>Both eyes: innumerable hard and confluent soft drusen in midperipheral retina, macular drusen PED, surrounded by crystalline drusen</td>
<td>p.Ile184fsX</td>
<td>Tyr/His</td>
</tr>
<tr>
<td>B-II:1/47/F</td>
<td>52</td>
<td>20/17</td>
<td>20/24</td>
<td>Both eyes: macular drusen with barely discernable (mid)peripheral drusen, clearly visualized on fluorescein angiography</td>
<td>p.Lys204fsX</td>
<td>Tyr/His</td>
</tr>
<tr>
<td>C-II:4/55/M</td>
<td>58</td>
<td>20/20</td>
<td>20/16</td>
<td>Both eyes: confluent soft drusen in posterior pole, surrounded by hard drusen</td>
<td>c.1697-17_-8del</td>
<td>Tyr/Tyr</td>
</tr>
<tr>
<td>D/50/F</td>
<td>61</td>
<td>20/35</td>
<td>20/50</td>
<td>Both eyes: innumerable small drusen in posterior pole</td>
<td>None</td>
<td>Tyr/His</td>
</tr>
<tr>
<td>E/54/F</td>
<td>60</td>
<td>20/20</td>
<td>20/25</td>
<td>Both eyes: innumerable small drusen scattered throughout retina</td>
<td>None</td>
<td>His/His</td>
</tr>
<tr>
<td>F/49/F</td>
<td>54</td>
<td>20/25</td>
<td>20/25</td>
<td>Both eyes: confluent macular drusen, drusenoid PED, patches of chorioretinal atrophy</td>
<td>None</td>
<td>Tyr/His</td>
</tr>
<tr>
<td>G/46/F</td>
<td>57</td>
<td>20/25</td>
<td>LP</td>
<td>OD: confluent macular drusen surrounded by small drusen, drusenoid PED OS: fibrotic scar</td>
<td>None</td>
<td>His/His</td>
</tr>
<tr>
<td>H/55/F</td>
<td>57</td>
<td>20/33</td>
<td>20/33</td>
<td>Both eyes: confluent macular drusen surrounded by small drusen</td>
<td>None</td>
<td>Tyr/His</td>
</tr>
<tr>
<td>I/5/F8</td>
<td>71</td>
<td>20/33</td>
<td>20/25</td>
<td>OD: innumerable small drusen scattered throughout retina, small classic CNV OS: innumerable small drusen scattered throughout retina, drusenoid PED</td>
<td>None</td>
<td>Tyr/His</td>
</tr>
<tr>
<td>J/68/M</td>
<td>75</td>
<td>20/25</td>
<td>20/80</td>
<td>OD: macular small drusen in posterior pole OS: macular small drusen in posterior pole, large classic CNV</td>
<td>None</td>
<td>His/His</td>
</tr>
<tr>
<td>K/48/M</td>
<td>74</td>
<td>20/20</td>
<td>20/25</td>
<td>Both eyes: innumerable small drusen in posterior pole</td>
<td>None</td>
<td>Tyr/His</td>
</tr>
<tr>
<td>L/65/F</td>
<td>68</td>
<td>20/33</td>
<td>20/1200</td>
<td>OD: confluent macular drusen surrounded by small drusen, drusenoid PED OS: central GA surrounded by small drusen</td>
<td>None</td>
<td>His/His</td>
</tr>
<tr>
<td>M/55/M</td>
<td>55</td>
<td>20/16</td>
<td>20/16</td>
<td>Both eyes: extensive small drusen in posterior pole</td>
<td>None</td>
<td>His/His</td>
</tr>
<tr>
<td>N/.../F</td>
<td>38</td>
<td>20/20</td>
<td>20/20</td>
<td>Both eyes: extensive soft drusen in posterior pole, numerous small peripheral drusen</td>
<td>None</td>
<td>Tyr/His</td>
</tr>
<tr>
<td>O/67/F</td>
<td>71</td>
<td>20/20</td>
<td>20/20</td>
<td>Both eyes: innumerable small drusen scattered throughout retina</td>
<td>None</td>
<td>Tyr/His</td>
</tr>
<tr>
<td>P/68/F</td>
<td>70</td>
<td>20/20</td>
<td>20/40</td>
<td>OD: innumerable small drusen in midperipheral retina, classic CNV OS: innumerable small drusen in midperipheral retina</td>
<td>None</td>
<td>Tyr/His</td>
</tr>
<tr>
<td>Q/43/F</td>
<td>48</td>
<td>20/25</td>
<td>20/100</td>
<td>Both eyes: confluent macular drusen surrounded by small drusen, drusenoid PED, patches of chorioretinal atrophy</td>
<td>None</td>
<td>Tyr/His</td>
</tr>
<tr>
<td>R/62/F</td>
<td>63</td>
<td>20/50</td>
<td>20/60</td>
<td>Both eyes: central GA surrounded by small drusen</td>
<td>None</td>
<td>Tyr/His</td>
</tr>
<tr>
<td>S/.../M</td>
<td>43</td>
<td>20/20</td>
<td>20/20</td>
<td>Both eyes: small drusen scattered throughout retina</td>
<td>None</td>
<td>His/His</td>
</tr>
<tr>
<td>T/45/F</td>
<td>52</td>
<td>20/33</td>
<td>20/50</td>
<td>Both eyes: innumerable small drusen scattered throughout retina</td>
<td>None</td>
<td>Tyr/Tyr</td>
</tr>
<tr>
<td>U/63/M</td>
<td>75</td>
<td>20/25</td>
<td>20/25</td>
<td>Both eyes: central pseudovitelliform lesion surrounded by innumerable small drusen</td>
<td>None</td>
<td>Tyr/His</td>
</tr>
</tbody>
</table>

Abbreviations: CNV, choroidal neovascularization; ellipses, no visual loss reported; GA, geographic atrophy; His, histidine; LP, light perception; OD, right eye; OS, left eye; PED, pigment epithelial detachment; Tyr, tyrosine.

a Tyr represents the wild-type allele, and His represents the risk allele.
A renal biopsy in patient C-II:4 at 27 years of age showed MPGN type II, resembling the findings in patient B-II:1. At age 46 years, end-stage kidney disease and subsequent renal failure necessitated a renal transplant. At the time of the most recent ophthalmic investigation, at age 58 years, there was no hematuria or proteinuria; the serum creatinine level was 1.10 mg/dL. In the 2 other carriers (C-II:2 and C-III:1) of the c.1697-17_-8del mutation, we observed no fundus abnormalities and no signs of renal failure on blood test results.

COMMENT

A subgroup of approximately 10% of patients with AMD are found to have BLD at the initial examination, that is, innumerable small hard drusen throughout the fundus that are hyperfluorescent on fluorescein angiography, resulting in a typical stars-in-the-sky appearance (J.P.H.V, C.J.F.B., L.H.H., B.J.K., A.I.D., and C.B.H., unpublished data, January 2012). The age at onset of BLD is typically earlier than that for regular AMD, and BLD are often observed in asymptomatic family members.25 The location and histopathological composition of BLD appear to be identical to the drusen found in typical AMD.30 A common mechanism of drusen biogenesis is therefore likely.

An association of the p.Tyr402His variant in the CFH gene with both AMD and the subtype of BLD has been previously described and confirmed by several studies.10-12,24,31 In addition, Boon and coworkers25 were the first to find pathogenic heterozygous mutations in the
CFH gene in association with the BLD phenotype. In their study, the development of BLD in individuals who carry a CFH mutation on one allele in combination with the presence of the p.Tyr402His variant on the other allele is described. We confirm this disease-causing model by heterozygous CFH gene mutations in a subgroup of patients affected with BLD. However, the mode of inheritance of these mutations was not apparent in any of the families. Our study was not consistently in accordance with the suggested disease model of compound heterozygosity with the p.Tyr402His variant because 5 of 10 patients did not carry the CFH mutation in association with the p.Tyr402His variant on the other allele. However, we cannot exclude that heterozygous CFH mutations will cause BLD and/or MPGN type II only when co-inherited with as-yet-undefined variants in other genes.

The segregation of mutations in families A and B appears to be consistent with an autosomal dominant inheritance pattern. At age 18 years, the youngest member of family A (A-III:4), who carries a CFH gene mutation, showed only peripheral soft drusen without the typical hard drusen seen in patients with BLD. Because the formation of drusen is related to age, this patient may develop more drusen in the future in accordance with the BLD phenotype. In family C, 1 individual of the 3 mutation carriers was affected, suggesting reduced penetrance of the CFH mutation or digenic/multigenic inheritance of variants in other genes. Alternatively, it is possible that a combination of genetic and acquired defects in the complement system may cause the disease, as has been demonstrated for MPGN.32,33

Together with a previous report on BLD caused by CFH gene mutations,25 our findings suggest that only patients having specific gene mutations will develop this clinical phenotype of BLD or have a greater genetic predisposition to develop BLD. This is in contrast to typical AMD, which is a multifactorial disorder caused by accumulating genetic and environmental factors.

### Table 2. Clinical and Genetic Characteristics of 3 Families Carrying a CFH Mutation

<table>
<thead>
<tr>
<th>Patient Code/ Age at Onset, y/Sex</th>
<th>Visual Acuity</th>
<th>Retinal Phenotype</th>
<th>CFH Mutation</th>
<th>CFH p. Tyr402His, Allele 1/Allele 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-III:2/. . /F</td>
<td>63</td>
<td>OD: normal</td>
<td>p.Lys204fsX</td>
<td>Tyr/His</td>
</tr>
<tr>
<td>A-III:1/. . /M</td>
<td>54</td>
<td>OD: hyperpigmented macular scar</td>
<td>None</td>
<td>His/His</td>
</tr>
<tr>
<td>B-III:1/. . /F</td>
<td>52</td>
<td>OD: normal</td>
<td>None</td>
<td>Tyr/His</td>
</tr>
<tr>
<td>B-III:2/. . /M</td>
<td>58</td>
<td>OD: normal</td>
<td>None</td>
<td>Tyr/His</td>
</tr>
<tr>
<td>C-III:1/. . /M</td>
<td>43</td>
<td>OD: normal</td>
<td>None</td>
<td>Tyr/His</td>
</tr>
</tbody>
</table>

Abbreviations: A, amblyopia; ellipses, no visual loss reported; His, histidine; NA, no visual acuity available; OD, right eye; OS, left eye; P, proband; PED, pigment epithelial detachment; T, old toxoplasma gondii infection; Tyr, tyrosine.

*b Probands are indicated parenthetically after the patient code.

*b Tyr represents the wild-type allele, and His represents the risk allele.
set of BLD compared with typical AMD. In our study, the 10 affected individuals with BLD who carried mutations in the CFH gene showed a heterogeneous clinical presentation. A robust genotype-phenotype correlation of the severity of the disease is therefore not possible because only the identified CFH mutations were taken into consideration.

Besides BLD, specific mutations in the CFH gene can also cause MPGN type II (dense deposit disease). However, the mutations we describe in this study are novel and, to our knowledge, have never been identified in patients with MPGN type II. To date, only 9 patients with MPGN type II have been reported to carry CFH mutations, and nearly all of them were homozygous or compound heterozygous for missense mutations in CFH. Only 1 patient was reported to carry a single heterozygous missense mutation and to develop late-onset MPGN type II and BLD. Because of the relatively late onset of MPGN type II in the 2 patients (B-II:1 and C-II:4) of our families, we reason that single heterozygous mutations in CFH may cause late-onset MPGN type II. Given that patient B-II:1 had early-onset BLD at the initial examination before renal disease was diagnosed, we recommend that patients with extensive early-onset BLD undergo screening for renal dysfunction. Despite urea and creatinine clearance within reference limits, MPGN and future renal dysfunction might develop because MPGN may be at a subclinical stage.

Fundus changes in patients with MPGN type II vary from pigmentary changes and BLD to larger soft drusen and CNV, finally leading to visual loss. The 2 cases reported in our study are the second and third reported in the literature who developed a triad of MPGN type II, BLD, and CNV caused by a specific mutation in CFH.
Figure 5. Retinal phenotype of patient C-II:4, carrier of the CFH.p.Lys204fsX frameshift mutation. Fundus photography of the right eye showed, besides the extensive drusen in the posterior pole extending to the peripheral retina of patients B-II:1 (A), B-II:4 (B), and B-II:6 (C). The green line indicates the optical coherence tomography section. Fluorescein angiography of patient B-II:4 showed similar but more numerous lesions (D) compared with color photography (B). Optical coherence tomography (oblique section) showed small dome-shaped elevations of the retinal pigment epithelium (E).

Figure 4. Retinal phenotypes of patients carrying the CFH.p.Lys204fsX frameshift mutation. Fundus photography of the right eyes showed extensive drusen in the posterior pole extending to the peripheral retina of patients B-II:1 (A), B-II:4 (B), and B-II:6 (C). The green line indicates the optical coherence tomography section. Fluorescein angiography of patient B-II:4 showed similar but more numerous lesions (D) compared with color photography (B). Optical coherence tomography (oblique section) showed small dome-shaped elevations of the retinal pigment epithelium (E).
In both cases, the CNV was effectively treated with intravitreal injections of bevacizumab.

With upcoming treatment modalities to target specific components of the complement system, early identification of the BLD subgroup of patients with AMD becomes relevant. The strong association of this group of patients with complement abnormalities may translate into a better response to complement-blocking therapy than among patients with AMD in general. Treatment with a humanized monoclonal antibody that blocks complement activity was shown to be successful in a patient with atypical hemolytic uremic syndrome. Humanized monoclonal antibodies can inhibit the overactivated complement system. For this reason, humanized monoclonal antibody seems to be a rational candidate treatment for patients with BLD caused by mutations in the \( CFH \) gene.

In summary, our findings confirm the important role of heterozygous mutations in the \( CFH \) gene in the development of BLD. The genotype-phenotype correlation is not straightforward, and other genetic and possibly environmental factors may contribute to the development or severity of the disease. We recommend monitoring the renal function in patients with extensive BLD because some of these patients may develop MPGN type II. Conversely, ophthalmic screening for BLD in patients with MPGN type II is recommended because of the risk of developing CNV and/or geographic atrophy. The association of heterozygous \( CFH \) mutations and presumed ensuing complement dysfunction in patients with AMD who also have BLD provides us with a promising target for future treatments.

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