Distinct Genetic Risk Profile of the Rapidly Progressing Diffuse-Trickling Subtype of Geographic Atrophy in Age-Related Macular Degeneration (AMD)

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PURPOSE. To genetically characterize a subphenotype of geographic atrophy (GA) in AMD associated with rapid progression and a diffuse-trickling appearance on fundus autofluorescence imaging.

METHODS. Patients from the Fundus Autofluorescence in Age-Related Macular Degeneration Study were phenotyped for diffuse-trickling GA (dt-GA; n = 44). DNA was analyzed for 10 known AMD-associated genetic variants. A genetic risk score (GRS) was calculated and compared with patients with nondiffuse-trickling GA (ndt-GA; n = 311) and individuals from the 1000 genomes project (1000G; n = 267). Given the phenotypic overlap between diffuse-trickling and late-onset retinal degeneration (LORD), all C1QTNF5 exons and their exon/intron boundaries were sequenced.

RESULTS. A statistically significant difference in allele frequencies between dt-GA and ndt-GA were found for CFH:rs1061170 and CFH:rs800292 (P_corrected = 0.03). The ARMS2 variant rs10490924 was significantly more frequent in dt-GA than in 1000G individuals (P_corrected < 0.01). The GRS of dt-GA patients was in-between the score of the 1000G individuals and that of patients with ndt-GA, significantly differing from both (P_corrected < 0.01). Sequencing of C1QTNF5 revealed 28 unique variants although none showed a statistically significant association with dt-GA when compared with 1000G individuals.

CONCLUSIONS. The dt-GA phenotype shows a remarkably different genetic risk profile from other GA phenotypes secondary to AMD. Disease-associated C1QTNF5 mutations were not identified. Together, these results suggest that the dt-GA phenotype is associated with a genetic background substantially different from other GA phenotypes and underlines the necessity to refine the clinical phenotyping, specifically when aiming for individualized therapies in AMD.

Keywords: AMD, fundus autofluorescence imaging, diffuse-trickling phenotype, late-onset retinal degeneration, C1QTNF5 gene, genetic risk factors
Recent developments in retinal imaging technologies allow for a more refined phenotyping of various retinal diseases and have been shown useful to discriminate subphenotypes of GA. In the context of the prospective natural history Fundus Autofluorescence in Age-Related Macular Degeneration (FAM) Study (ClinicalTrials.gov Identifier: NCT00393692), the so-called diffuse-trickling GA (dt-GA) variant was identified by comparative fundus autofluorescence imaging (FAF) and was classified as a subtype of AMD. Several characteristic features discriminate this distinct GA phenotype from other AMD-related GA subtypes including (1) a significantly faster disease progression (i.e., enlargement rates of atrophic areas), (2) a lobular configuration of the atrophic patches, that exhibit a grayish FAF signal, (3) a significantly thinner choroid, and (4) a marked separation of the RPE/Bruch’s membrane complex in spectral-domain optical coherence tomography (SD-OCT) imaging, which was interpreted as excessive diffuse accumulation of sub-RPE deposits (Fig. 1). Besides the morphologic characteristics, patients with the dt-GA subtype differ from patients with other AMD-related GA phenotypes by a significantly younger age at first presentation and a higher prevalence of cardiovascular comorbidity. These discriminating findings have led to the hypothesis that a differential pathogenesis is underlying the dt-GA phenotype and have challenged the diagnosis of AMD.

In fact, there is phenotypic overlap with disease entities other than AMD. Extensive macular atrophy with pseudodrusen-like appearance (EMAP) exhibits a very similar or even the same phenotype and there is high resemblance with characteristics described in age-related choroidal atrophy (ARCA). Furthermore, there are striking similarities of the dt-GA phenotype with the retinal degeneration described in patients with late-onset retinal degeneration (LORD) (Fig. 1). While no genetic causes have been identified for EMAP and ARCA so far, autosomal-dominant inheritance is well established for LORD (OMIM: 605670). Which was found to be associated with a single Ser163Arg missense mutation in the globular C1q domain of the C1q and TNF-related protein 5 (C1QTNFS) gene. A membrane-associated and secretory protein in the RPE and ciliary body and the S163R mutation of C1QTNFS impairs its secretion and appears to display a significant reduction in implementing RPE cellular adhesion. A key pathologic feature in LORD is a diffuse thick extracellular sub-RPE deposit.

In the present work, we aimed to determine the genetic background of the dt-GA subphenotype and GA of other phenotypes secondary to AMD. Due to phenotypic overlap between dt-GA and LORD we additionally performed a candidate gene approach by analyzing the C1QTNFS gene.

### METHODS

#### Ethics Statement

The study followed the tenets of the Declaration of Helsinki and was approved by the local Ethics Review Board at the University of Bonn, Bonn, Germany (ID: 197/12), and the Department of Ophthalmology, University of Würzburg, Würzburg, Germany (ID: 78/01). Informed written consent was obtained from each patient after explanation of the nature and possible consequences of the study.

### Study Characteristics

Study characteristics are summarized in Table 1. Forty-four patients with the dt-GA subphenotype were recruited as part of the FAM study (in the public domain, www.clinicaltrials.gov: NCT00393692), and its extension trial, the Directional Spread in Geographic Atrophy (DSGA) study (NCT02051998). Both have been described in detail elsewhere. Briefly, patients needed to be above 50 years of age (55 years for DSGA) at the time of inclusion and had to exhibit GA in at least one eye. Clear ocular media that allowed for good-quality imaging had to be present. Exclusion criteria included any history of retinal surgery, laser photocoagulation, and radiation therapy or other retinal disease in the study eye, including diabetic retinopathy. Furthermore, 311 patients with GA but without the dt-GA subtype were recruited in Würzburg and Bonn, equally as part of the FAM study. Blood samples were taken from each patient after informed consent was given. Additionally, we included data from a total of 267 European subjects (Utah Residents with Northern and Western European Ancestry [CEU], British in England and Scotland [GBR], and Finnish in Finland [FIN]) from the 1000 Genomes project (1000G; Release 20110521, in the public domain, http://www.1000genomes.org, accessed May 2, 2012).

### Definition of GA due to AMD

Geographic atrophy was defined funduscopically as one or more well-defined, usually more or less circular patches of partial or complete depigmentation of the RPE, typically with visualization of underlying large choroidal blood vessels. In the FAM and DSGA-studies, GA due to AMD was further defined as sharply demarcated lesions with clearly reduced fundus autofluorescence (FAF) signal of an extend of greater than or equal to 0.05 mm² (approximately 178 µm in diameter) that is not caused by masking effects of exudative retinal changes (e.g., bleeding, exudation, fibrotic scar). Additionally, the affected eye should have funduscopically visible soft drusen and/or retinal pigment abnormalities consistent with AMD.

### Definition of the dt-GA Phenotype

Phenotyping of GA was described in detail elsewhere. In brief, the previously introduced classification of GA based on abnormal FAF patterns, was used to identify the specific FAF phenotype of each eye by two independent graders (MF, SSV) and a third reader (FGH) in case of discrepancy.

The dt-GA phenotype was characterized in FAF images by coalescent lobular atrophic lesions with an atrophic area appearing rather grayish compared with the dark black appearance of outer retinal atrophy seen in other GA subtypes. Adjacent to atrophic patches, the FAF signal is markedly enhanced with a diffuse trickling FAF signal toward the periphery. Funduscopically, eyes with the FAF pattern characteristic of dt-GA exhibit dense granular hyperpigmentation in the central macula and the border areas of the atrophic lesions appear hyperpigmented. Furthermore, adjacent to the atrophic lesions, there are small yellowish spots. Reticular pseudodrusen are present, whereas soft drusen are rather infrequent in this phenotype. Spectral-domain OCT imaging shows an obvious separation of the RPE/Bruch’s membrane complex (Fig. 1). If there was suspicion of exudative AMD based on funduscopy (SD-OCT or FAF-imaging), fluorescein angiography

### Table 1. Study Characteristics

<table>
<thead>
<tr>
<th></th>
<th>dt-GA</th>
<th>1000G EUR</th>
<th>ndt-GA</th>
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<tbody>
<tr>
<td>Number of individuals</td>
<td>44</td>
<td>267</td>
<td>311</td>
</tr>
<tr>
<td>Mean GRS (SD)</td>
<td>0.82 (1.69)</td>
<td>0.00 (1.36)</td>
<td>1.63 (1.34)</td>
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<td>Mean age (SD)</td>
<td>67.20 (11.28)</td>
<td>NA</td>
<td>78.76 (6.57)</td>
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<tr>
<td>Fraction of males, %</td>
<td>36.36</td>
<td>54.49</td>
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FIGURE 1. Fundus autofluorescence imaging and OCT imaging of eyes classified as dt-GA. There is variable extent of degeneration and variability in age of patients ([A] 69-year-old male, [B] 71-year-old male, [C] 50-year-old female, and [D] 58-year-old female). Common findings are coalescent lobular atrophic lesions with an atrophic area appearing grayish on FAF imaging. Optical coherence tomography imaging reveals a thin choroid and a marked separation of the RPE/Bruch’s membrane complex. Eyes classified with dt-GA may phenotypically overlap with ARCA, EMAP, and LORD.
was performed. Eyes were excluded from the analysis if a neovascular phenotype was verified.

**Genotyping and GRS**

Genotyping was performed as described previously. Briefly, genomic DNA was extracted from peripheral blood leukocytes by established methods. Genotyping was performed by TaqMan SNP genotyping (Applied Biosystems, Foster City, CA, USA) or by PCR followed by restriction enzyme digestion (New England Biolabs, Ipswich, MA, USA) and subsequent restriction fragment length analysis (RFLP). The resulting genotypes were coded as the number of AMD risk increasing alleles (0, 1, or 2), that is alleles, which are more frequent in cases than in controls (Table 2). From these variants, we computed the GRS according to Grassmann et al. by including the weights obtained from the parsimonious model based on 10 single nucleotide polymorphisms (SNPs; Table 2). We only genotyped variants of the parsimonious 10 SNP model because it exhibited comparably classification accuracy as the 13 SNP model proposed by Grassmann et al. Furthermore, recent studies showed that additional inclusion of novel AMD-associated risk variants in such risk models contributes only marginally to classification accuracy and explained heritability. We subtracted 9.05 from all GRS values to center the distribution on zero for the 1000G samples. Additionally, univariate logistic test was used as implemented in R to evaluate differences in GRS between groups. Moreover, we used the ggplot function from the ggplot2 package in R to draw jitterplots. The Student’s t-test was used as implemented in R to evaluate differences in the GRS between groups. Additionally, univariate logistic regression was applied as implemented in R to evaluate the association of single variants with dt-GA. Furthermore, we used a Sequencing Kernel Association Test (SKAT) as implemented in the package ‘SKAT’ in R to assess the overall burden of rare and common variants on disease risk. The obtained raw P values were adjusted by a conservative Bonferroni correction.

**Statistical Analyses and Visualization**

We computed means and 95% confidence intervals (CIs) of the GRS in different groups and used the ggplot2 package in R to draw jitterplots. The Student’s t-test was used as implemented in R to evaluate differences in the GRS between groups. Additionally, univariate logistic regression was applied as implemented in R to evaluate the association of single variants with dt-GA. Furthermore, we used a Sequencing Kernel Association Test (SKAT) as implemented in the package ‘SKAT’ in R to assess the overall burden of rare and common variants on disease risk. The obtained raw P values were adjusted by a conservative Bonferroni correction.

| Table 2. Frequency of Genetic Risk Variants in the Cohorts Investigated |
|-----------------|-------------|-----------------|-------------|-----------------|-------------|-----------------|-------------|
|                  | Odds Ratio | 95% CI (%)      | Raw P Value  | Corrected P Value | Odds Ratio | 95% CI (%)      | Raw P Value  | Corrected P Value | Frequency in 1000G EUR |
| APOE_rs429358    | 0.777      | 0.395-1.647     | 0.48        | 1                | 1.37       | 0.722-2.84      | 0.36        | 1                | 0.88         |
| APOE_rs7412      | 1.45       | 0.752-2.655     | 0.25        | 1                | 2.413      | 1.218-4.639     | 0.01        | 0.09             | 0.16         |
| ARM22_s10490924  | 0.876      | 0.566-1.337     | 0.55        | 1                | 2.357      | 1.453-3.916     | 0.001       | 0.01             | 0.39         |
| C3_r2220199      | 0.882      | 0.528-1.544     | 0.65        | 1                | 1.406      | 0.817-2.36      | 0.20        | 1                | 0.25         |
| CFB_rs4151667    | 0.367      | 0.119-1.372     | 0.10        | 1                | 1.073      | 0.409-3.682     | 0.90        | 1                | 0.95         |
| CFB_rs438999     | 0.342      | 0.149-0.843     | 0.14        | 0.923            | 0.446-1.566 | 0.84        | 1                | 0.91         |
| CFH_rs1061170    | 0.503      | 0.315-0.795     | 0.003       | 0.03             | 1.52       | 0.965-2.407     | 0.07        | 0.72             | 0.50         |
| CFH_rs6677604    | 0.545      | 0.305-1.011     | 0.04        | 0.45             | 0.815      | 0.468-1.49      | 0.48        | 1                | 0.82         |
| CFH_rs800292     | 0.394      | 0.216-0.736     | 0.003       | 0.03             | 1.641      | 0.947-3.015     | 0.09        | 1                | 0.82         |
| PLA2G12A_rs2285714 | 0.901   | 0.551-1.465     | 0.68        | 1                | 0.979      | 0.601-1.581     | 0.93        | 1                | 0.41         |
by multiplying the *P* values with the number of (independent) tests performed.

**RESULTS**

**Genetic Risk of AMD in dt-GA Patients**

To evaluate the genetic risk, we genotyped 10 known AMD associated genetic variants in 44 dt-GA patients and 311 patients with ndt-GA. Additionally, we extracted the genotypes for the 10 variants from 267 European individuals as given in the 1000G (Table 2). We found a statistically significant difference in the allele frequencies between dt-GA and ndt-GA for CFH_rs1061170 (*P*<sub>Corrected</sub> = 0.035) and CFH_rs800292 (*P*<sub>Corrected</sub> = 0.026) after adjustment for multiple testing. Strikingly, only a single variant (APOE_rs7412) had a higher frequency in dt-GA patients than in ndt-GA patients. Conversely, we performed a similar analysis and compared dt-GA cases with 1000G controls and found a nominally significant association of two SNPs, ARMS2_rs10490924 and APOE_rs7412 with disease. After adjustment for multiple testing, only ARMS2_rs10490924 remained statistically significant (*P*<sub>Corrected</sub> = 0.008).

To summarize the genetic risk, we computed the GRS<sup>11</sup> for the 1000G European individuals, for dt-GA patients and for patients with ndt-GA and found mean GRS values of 0.00 (95% CI: -0.16 to 0.16), 0.82 (95% CI: 0.32-1.32), and 1.63 (1.48-1.78), respectively (Fig. 2). The mean GRS in dt-GA patients was significantly lower than the mean GRS of ndt-GA patients (*P*<sub>Corrected</sub> = 0.01) but also significantly higher than the mean GRS of control subjects (*P*<sub>Corrected</sub> = 0.01). As expected, the mean GRS for ndt-GA patients was significantly higher than the GRS of control subjects (*P*<sub>Corrected</sub> < 1 x 10^-16). Because two variants in the *CFH* gene were significantly different between dt-GA and ndt-GA, we recalculated a GRS based on eight variants (excluding CFH_rs1061170 and CFH_rs800292). We found a nominally significant difference (*P* = 0.049) between the risk scores of dt-GA (mean: 0.53, 95% CI: 0.16-0.90) and
Next Generation Sequencing of the C1QTNF5 Gene and Association Testing

We sequenced the 15 exons and immediate flanking intronic regions of C1QTNF5 and obtained on average 135,984 (SD ± 65,610) reads per individual/library. The average read length was 182 bp (SD ± 51 bp) and the average coverage was 6541 (SD ± 5634) reads. In total, we found 28 unique variants in the C1QTNF5 gene in 44 dt-GA patients. We compared the frequencies of these variants with the frequencies observed in the 1000G samples (Table 3). We fitted univariate logistic regression models for each variant and found three variants with nominally significant association with dt-GA. After adjustment for multiple testing none of the variants remained statistically significant.

To test whether the dt-GA phenotype could result from distinct mutations within the C1QTNF5 gene, we compared the total frequency of variants in the gene between dt-GA individuals and the 1000G controls. This corresponds to an average of 4.14 (SD ± 1.77) and 4.70 (SD ± 1.89) variants per person, respectively, and is not significantly different in the two groups (P > 0.05). To assess the overall burden of genetic variation in the C1QTNF5 gene in dt-GA risk, we analyzed all identified variants in a SKAT by comparing the genotypes of dt-GA and ndt-GA patients with the genotypes obtained from the 1000G in the C1QTNF5 gene. We found no statistically significant difference in the genetic burden of variants in C1QTNF5 (P > 0.05).
**DISCUSSION**

Here, we demonstrate that the dt-GA phenotype in late stage AMD shows remarkable genetic differences from other FAF-defined GA phenotypes. In addition, despite clinical similarities between dt-GA and autosomal dominant LORD such as excessive accumulation of hyperreflective material between the RPE and Bruch’s membrane,\cite{15,21,42} no disease-associated variants were detected in the LORD-associated C1QTNF5 gene.

From 10 prominent variants known to be strongly associated with AMD risk, two of these, namely CFH_rs1061170 and CFH_rs800292, revealed a statistically significant difference in their allele frequencies between dt-GA and ndt-GA. Furthermore, there was a single variant, ARMS2_rs10490924, significantly associated with dt-GA when comparing the frequency with 1000G individuals. Calculating a GRS as previously described\cite{11} revealed a genetic risk profile of dt-GA individuals significantly different from both, ndt-GA and 1000G individuals. With a GRS of 0.88 the genetic risk of dt-GA was in-between that of 1000G and ndt-GA individuals. Together, these findings suggest that genetic factors, which may act in dt-GA are likely distinct from those responsible for other phenotypes of GA secondary to AMD, especially because those known factors only explain a small proportion of the observed disease risk variance in dt-GA. These findings are in line with recent findings, which provide evidence for substantial clinical differences between dt-GA and ndt-GA.\cite{15,16,18,43}

The question arises whether variant ARMS2_rs10490924, previously reported to significantly influence the progression rate of GA lesions\cite{39}, could account for the faster GA growth in dt-GA versus ndt-GA patients.\cite{15,17,18} Our data show, however, that the frequency of the ARMS2_rs10490924 variant in dt-GA patients is similar to the frequency in ndt-GA patients. This is also true for the C3_rs2230199 variant, also known to be a risk factor for GA lesion growth.\cite{43} These findings suggest that the two variants associated with disease progression likely have no role in the differences in lesion growth rate between dt-GA and ndt-GA patients. Other so far unknown factors, genetic or environmental, appear to play a role in the different pathologies of DT-GA and NDT-GA.

The molecular analysis of the C1QTNF5 gene in DTGA patients was stimulated by the phenotypic overlap of DTGA with the retinal degeneration in patients diagnosed with LORD. Most strikingly, the two disease pathologies share an excessive accumulation of hyperreflective material between the RPE and Bruch’s membrane as visualized by SD-OCT imaging.\cite{15,21,42} no disease-associated variants were detected in the LORD-associated C1QTNF5 gene. Most strikingly, the two disease pathologies share an excessive accumulation of hyperreflective material between the RPE and Bruch’s membrane,\cite{15,21,42} no disease-associated variants were detected in the LORD-associated C1QTNF5 gene. From 10 prominent variants known to be strongly associated with AMD risk, two of these, namely CFH_rs1061170 and CFH_rs800292, revealed a statistically significant difference in their allele frequencies between dt-GA and ndt-GA. Furthermore, there was a single variant, ARMS2_rs10490924, significantly associated with dt-GA when comparing the frequency with 1000G individuals. Calculating a GRS as previously described\cite{11} revealed a genetic risk profile of dt-GA individuals significantly different from both, ndt-GA and 1000G individuals. With a GRS of 0.88 the genetic risk of dt-GA was in-between that of 1000G and ndt-GA individuals. Together, these findings suggest that genetic factors, which may act in dt-GA are likely distinct from those responsible for other phenotypes of GA secondary to AMD, especially because those known factors only explain a small proportion of the observed disease risk variance in dt-GA. These findings are in line with recent findings, which provide evidence for substantial clinical differences between dt-GA and ndt-GA.\cite{15,16,18,43}

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A phenotypic overlap of two diseases may not necessarily reflect a shared etiology but may be expression of a common final pathway of different pathogeneses. Therefore, dt-GA, LORD, EMAP, and ARCA may be unrelated diseases with a similar unspecific end-stage phenotype. On the other hand, it cannot be excluded that these diseases share a common etiology with slightly differing end-stage manifestation. It is noteworthy that patients who were classified to exhibit the dt-GA phenotype show variable extend of degeneration and a relatively high variability in age of onset. Therefore, the diffuse-trickling phenotype may comprise patients with EMAP, ARCA, and LORD. Indeed, one diffuse-trickling patient had been excluded from the current analysis because of detection of the LORD associated mutation C1QTNF5:c.489C > G.

Whether the diffuse-trickling phenotype can be classified as AMD remains debatable. There are distinct characteristics that discriminate the diffuse-trickling phenotype from typical AMD. Here, we additionally demonstrate that dt-GA genetically differs from other GA subtypes secondary to AMD. Together, these findings strongly suggest that differential pathogenetic pathways are operative in distinct clinical phenotypes of GA, at least between dt-GA and ndt-GA. This underscores the importance of refined phenotyping particularly in the context of designing interventional clinical trials for AMD targeting specific pathways.

It is anticipated that with the ongoing development of retinal imaging techniques, further subtypes of AMD will be identified with differential pathogeneses when compared with typical AMD. The concept where AMD represents a disease spectrum rather than a homogenous entity appears appealing.\cite{44}

To the best of our knowledge, this study demonstrates for the first time a difference in the genetic profile between dt-GA and other GA subtypes due to AMD. The candidate gene approach examining the C1QTNF5 gene as an excellent candidate gene due to phenotypic overlaps in disease pathology failed to further elucidate the genetic background of dt-GA. Further approaches to identify the true genetic cause of dt-GA will include refined clinical phenotyping and possibly further analysis of C1QTNF5 and related genes.

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**References**


To Characterize a Subphenotype of GA in AMD


