A Subgroup of Age-Related Macular Degeneration is Associated With Mono-Allelic Sequence Variants in the ABCA4 Gene

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**PURPOSE.** Age-related macular degeneration (AMD) is a heterogeneous condition of high prevalence and complex etiology involving genetic as well as environmental factors. By fundus autofluorescence (FAF) imaging, AMD can be classified into several distinct phenotypes, with one subgroup characterized by fine granular pattern with peripheral punctate spots (GPS[+]). Some features of GPS[+] overlap with Stargardt disease (STGD1), a recessive macular dystrophy caused by biallelic sequence variants in the ATP-binding cassette transporter 4 (ABCA4) gene. The aim of this study was to investigate the role of ABCA4 in GPS[+].

**METHODS.** The ABCA4 gene was sequenced in 25 patients with the GPS[+] phenotype and 29 with geographic atrophy (GA)-AMD but no signs of GPS (GPS[−]). In addition, frequencies of risk-increasing alleles at three known AMD susceptibility loci, including complement factor H (CFH), age-related maculopathy susceptibility 2 (ARMS2), and complement component 3 (C3), were evaluated.

**RESULTS.** We demonstrate that GPS[+] is associated significantly with monoallelic ABCA4 sequence variants. Moreover, frequencies of AMD risk-increasing alleles at CFH, ARMS2, and C3 are similar in GPS[+] and STGD1 patients, with risk allele frequencies in both subcategories comparable to population-based control individuals estimated from 3,510 individuals from the NHLBI Exome Sequencing Project.

**CONCLUSIONS.** Our data suggest that the GPS[+] phenotype is accounted for by monoallelic variants in ABCA4 and unlikely by the well-established AMD risk-increasing alleles at CFH, ARMS2, and C3. These findings provide support for a complex role of ABCA4 in the etiology of a minor proportion of patients with AMD. (Invest Ophthalmol Vis Sci. 2012;53:2112–2118) DOI:10.1167/iovs.11-8785

The ATP-binding cassette, subfamily A, member 4 (ABCA4, MIM 601691) gene encodes an integral transmembrane protein, which is expressed exclusively in retinal photoreceptors. It is involved in the clearance of all-transretinal aldehyde, a byproduct of the retinoid cycle of vision. A characteristic feature of ABCA4-associated pathology is the accumulation of lipofuscin and its constituent, diretinoid-pyridinium-ethanolamine (A2E), in the retinal pigment epithelium (RPE) known to affect cell function and viability. To date, biallelic variants in the ABCA4 gene have been associated with several retinal dystrophies, including autosomal recessive Stargardt disease (STGD1, [MIM 248200]), autosomal recessive cone-rod dystrophy 3 (arCRD, [MIM 601161]), and autosomal recessive retinitis pigmentosa 19 (arRP, [MIM 601718]). Classification of types of ABCA4 variants and correlation to severity of disease manifestations have suggested an inverse relationship between ABCA4 transporter activity and disease outcome. For example, a combination of null sequence variants causes arRP, a severe and early form of retinal dystrophy, while compound heterozygotes for a null variant and a variant resulting in partial ABCA4 activity present with a less severe condition, such as arCRD or STGD1. Consistent with such a model is the notion that a monoallelic variant in a carrier person may confer risk for age-related macular degeneration (AMD, [MIM 603075]), a genetically complex disorder of high frequency in the general population but with clinical features developing late in life, generally not before 65 years of age.

In an initial study, monoallelic variants in ABCA4 were associated with the non-exudative form of AMD. Subsequent reports failed to replicate these findings, although it became...
evident that very large proband groups would be required to reach statistical significance for the expected small difference in allele frequencies between cases and controls.\textsuperscript{31} In an alternative approach, pedigrees in which \textit{ABCA4} variants cosegregated with AMD in parents and grandparents of STGD1 probands were evaluated; however, the number of suitable families was insufficient to reach satisfactory statistical power.\textsuperscript{12,13} Similarly, genotype-phenotype studies on siblings of patients with AMD and known \textit{ABCA4} variants remained inconclusive.\textsuperscript{14}

In recent years, major progress was made in elucidating the genetic basis of AMD through the identification of two major susceptibility loci at 1q31 and 10q26, together likely accounting for approximately 50% of cases. At 1q31, strongly associated variants in the complement factor H (\textit{CFH}, MIM 134370) gene suggest an involvement of the complement cascade in AMD pathogenesis.\textsuperscript{15–18} Consequently, AMD risk variants in other genes involved in the complement cascade were identified, contributing to a minor extent to disease, for example complement component 2 (\textit{C2} [MIM 217000]) and the high temperature requirement factor A1 gene (\textit{HTRA1} [MIM 602194]).\textsuperscript{19,20} and complement factor I (\textit{CFI} [MIM 217030]).\textsuperscript{21} At the second major AMD risk locus at 10q26, disease association signals support a region harboring two genes in strong linkage disequilibrium, namely the age-related maculopathy susceptibility 2 gene (\textit{ARMS2} [MIM 611313]) and the high temperature requirement factor A1 gene (\textit{HTRA1} [MIM 602194]),\textsuperscript{22,23} although functional implications of the 10q26 locus on AMD pathiology still are unknown.

With the advent of improved imaging technology, intrinsic retinal fundus autofluorescence (FAF) can now be recorded in vivo at high resolution and with accurate topographic discrimination. The fluorescent bisretinoid A2E was shown to be the dominant fluorophore in FAF images, thus allowing a direct measure of functional importance for disease state.\textsuperscript{24} Blue laser FAF imaging by confocal scanning laser ophthalmoscopy (cSLO) offers the possibility to identify novel prognostic determinants in the context of advanced non-exudative AMD\textsuperscript{25} and provides a more refined phenotypic classification.\textsuperscript{26,27} AMD eyes showing widespread areas with increased FAF in the perilesional zone of areas with geographic atrophy (GA) are termed “diffuse.”\textsuperscript{25,26} This phenotype can be subdivided further based on the topographic pattern of abnormal FAF in five subgroups referred to as “reticular,” “branching,” “fine granular,” “trickling,” and “fine granular with peripheral punctate spots” (GPS\textsuperscript{[+]}).\textsuperscript{20}

As some FAF features of GPS\textsuperscript{[+]} overlap with STGD1,\textsuperscript{28} we aimed to investigate the variant status of the \textit{ABCA4} gene in this AMD subtype. We show that the GPS\textsuperscript{[+]} phenotype is associated strongly with monoallelic variants in \textit{ABCA4}. In contrast, this subgroup was not associated with the known frequent AMD risk-increasing alleles in the \textit{CFH}, \textit{ARMS2}, and \textit{C3} genes. Our findings suggest that monoallelic \textit{ABCA4} variants predispose to AMD, in particular to the GPS\textsuperscript{[+]} subphenotype, which represents approximately 2–5% of cases with geographic atrophy.

\section*{Methods}

\subsection*{Ethics Statement}

This study followed the tenets of the Declaration of Helsinki, and was approved by the Ethics Review Boards at the University of Bonn and Würzburg, Germany. Informed written consent was obtained from each patient after explanation of the nature and possible consequences of the study.

\section*{Patient Selection}

As part of a longitudinal natural history multicenter study (FAM Study, registration www.clinicaltrials.gov: NCT00395692), patients diagnosed with unilateral or bilateral GA due to AMD were screened for the GPS\textsuperscript{[+]} phenotype. Patients were recruited through the Departments of Ophthalmology at the University of Bonn, Bonn, Germany, and the University of Würzburg, Würzburg, Germany. These included patients with uni- or multifocal GA, \(\geq\) 50 years of age and with clear media to allow FAF imaging. Exclusion criteria were any history of retinal surgery, laser photoocoagulation and radiation therapy or other retinal disease in the study eye, including diabetic retinopathy or known hereditary retinal dystrophy. Ophthalmologic history, family history and possible risk factors were recorded. The age of onset was defined as either the patient’s age at which visual loss was first noted or the age documented in an ophthalmic record of the first diagnosis.

FAF was recorded with a confocal scanning laser ophthalmoscope (Heidelberg Retina Angiograph - HRA classic and HRA 2, Heidelberg Engineering, Heidelberg, Germany).\textsuperscript{29} (On FAF recordings, areas of GA were readily identified based on a corresponding area of markedly reduced FAF signal due to the absence of the RPE cell monolayer.\textsuperscript{27} Images were evaluated based on an established classification scheme for abnormal FAF in the perilesional zone of GA.\textsuperscript{26}

A total of 25 GA patients (11 males, 14 females) displayed a bilateral GPS\textsuperscript{[+]} phenotype. The mean age of onset was 63.6 \(\pm\) 10.4 years (range 50 to 84 years). To define a similar-sized GPS\textsuperscript{[−]} control group, we selected two patients randomly from each of seven remaining FAF pattern subgroups (\(n = 14\)), that is “none,” “focal,” “diffuse-trickling,” “diffuse-reticular,” “diffuse-fine-granular,” “diffuse-branishing,” and “banded.”\textsuperscript{26,29} Additionally, another 15 GA patients with no sign of the GPS\textsuperscript{[+]} phenotype were selected randomly from our GA cohort. Together, the GPS\textsuperscript{[−]} control group consisted of 12 males and 17 females. The mean age of onset in this group was 68.9 \(\pm\) 9.0 years (range 50 to 83 years). In the GPS\textsuperscript{[−]} group, 14 out of 25 patients reported a positive family history of retinal disease. In these families the pattern of inheritance was suggestive of a dominant mode. In contrast, only seven of 29 patients in the GPS\textsuperscript{[−]} group reported a positive family history.

As a reference cohort, 14 STGD1 patients (3 males and 11 females) were selected randomly from the routine diagnostics department at the Institute of Human Genetics (University of Regensburg, Regensburg, Germany). Informed consent was given by each patient to make the DNA sample available for research purposes. The mean age of disease onset in this group was 57.2 \(\pm\) 14.5 years (range 10 to 64 years).

\section*{ABCA4 Sequence Analysis and Evaluation of Variants Identified}

Genomic DNA was isolated for each patient from peripheral blood lymphocytes using standard extraction procedures. For sequence analysis of the \textit{ABCA4} gene, all coding exons were analyzed by direct Sanger sequencing\textsuperscript{30} after amplification of the 50 exons of the \textit{ABCA4} gene by PCR with flanking oligonucleotide primers (Supplementary Table S1, http://www.iovs.org/lookup/suppl/doi:10.1167/iovs.11-87851/DCSupplemental). The Big Dye Terminator Cycle Sequencing Kit Version 1.1 (Applied Biosystems, Darmstadt, Germany) was used according to the manufacturer’s instructions. Reactions were analyzed with an ABI Prism Model 3130xl Sequencer (Applied Biosystems).

Possible deleterious effects of identified variants were evaluated with MutationTaster (http://www.mutationtaster.org),\textsuperscript{31} PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2),\textsuperscript{32} and MutPred (http://mutpred.mutdb.org).\textsuperscript{33} In addition, neutral and intron sequence changes at the \textit{ABCA4} locus not affecting the canonical splice-acceptor or splice-donor sites were analyzed for their likelihood of creating or destroying splice sites using the Alamut Mutation Interpretation Software (Interactive Biosoftware, Rouen, France). All variants were described according to current nomenclature guidelines (http://www.
hgv.org/mutnomen), assigning the A of the first ATG translational initiation codon as nucleotide +1.

Variants were classified as “benign” and were excluded from further analysis when (i) the minor allele frequency (MAF) was ≥0.03 in any of the 13 populations of the 1000Genomes Project with N ≥50 (October 2011 data release; http://www.1000genomes.org) or of the NHLBI Grand Opportunity Exome Sequencing Project (ESP 5400 exome data initial release [November 22, 2011]; https://esp.gs.washington.edu/drupal), or (ii) the MAF was below 0.03 or unknown and the alteration was synonymous but none of the prediction programs predicted effects on splicing or disease pathology. The remaining variants with MAF below 0.03 or unknown frequency were classified as “uncertain variants” (UVs) when prediction of pathogenicity or potential splice site changes were inconclusive, “likely pathogenic” when the predictions were conclusive, and “pathogenic” when it resulted in a nonsense or a frameshift alteration or affected an invariant splice site position (Supplementary Tables S2 and S3).

**Genotyping of AMD Risk Alleles**

Three common AMD risk alleles in CFH (rs1061170:T>C), ARMS2 (rs10490924:T>G), and C3 (rs2230199:C>G) were determined by direct sequencing of the respective genomic regions (Supplementary Table S4). Statistical analyses were carried out with the R.35

**RESULTS**

GA-AMD patients with FAF phenotypes referred to as “fine granular with peripheral punctate spots” (GPS[+]), Fig. 1) revealed an age of onset that is not significantly different from GPS[−] patients (P = 0.055, Student’s t-test, two-sided) but significantly different from patients diagnosed with typical STGD1 (P < 0.001, Fig. 2). Interestingly, FAF images in GPS[+] showed striking resemblance to those recorded in STGD1 patients (Fig. 3). This prompted us to analyze the 50 exons of the ABCA4 gene for sequence alterations in 25 probands with the GPS[+], and compare those findings to sequencing results of 29 GA-AMD and 14 STGD1 patients. A total of 57 distinct variants was identified in the 68 patients analyzed. These variants were classified into four groups based on criteria, such as frequency in general populations, deleterious effects on the protein level as predicted from bioinformatics tools, and predicted effects of synonymous coding and intronic sequence alterations on transcript splicing.

**Figure 1.** Classification of abnormal fundus autofluorescence (FAF) in the perilesional zone of GA due to AMD, based on FAF features in the area surrounding the atrophic lesion (black central lesion). The “diffuse” FAF pattern is divided into five subgroups, including the “GPS[+]” pattern. This particular phenotype is characterized by diffuse FAF changes in the form of elongated small lesions with highly increased FAF signals. The lesions are variable in size, shape and number, often with small adjacent zones of decreased FAF.

**Figure 2.** Characteristics of age of onset in patients with AMD phenotypes GPS[+] and GPS[−] as well as in patients with STGD1. Boxes represent 50% quartiles. Whiskers indicate minimal and maximal age of onset. Thick lines represent the corresponding median. (GPS[+] vs. GPS[−]; P = 0.055; GPS[+] vs. STGD1: P < 0.001).

**Figure 3.** Comparison of FAF pattern between the GPS[+] phenotype and STGD1. **Upper row:** Right and left eye of a female patient (age of onset 46 years) with autosomal recessive STGD1 genetically confirmed by two ABCA4 variants (c.2588G>C, p.G863A/p.G863del and c.4254C>T, p.E1412X). The FAF phenotype is characterized by elongated small lesions with highly increased or reduced signals. The patient exhibits bilateral central atrophy (large black lesion). **Lower row:** Right and left eyes of a 59-year-old male patient (M07-038-11.085) with the GPS[+] phenotype and age of onset at 56 years. The FAF phenotype resembles the findings in the STGD1 patient (upper row). The patient carries a heterozygous, complex disease allele (c.1622T>C, p.L541P; c.3113C>T, p.A1038V) in the ABCA4 gene.
directly the cis configuration of the c.3113C>T / c.1622T>C alleles in one case by segregation analysis (patient M07-0338-11,085), these two variants have been shown repeatedly in previous studies to occur as a frequent complex allele on a single chromosome.\textsuperscript{10,36} Trans-configuration was confirmed for heterozygous changes c.5113C>T (p.A1058V) / c.5261A>C (p.E1087D) in patient L-099-GA. Due to lack of DNA from further family members, segregation of variants c.5113C>T (p.A1058V) / c.3752delA (p.Glu1251fs) and c.1804C>T (p.R602W) / c.1928T>G (p.V643G) could not be assessed further (Supplementary Table S5).

In the GPS[+] group, patient H-073-GA carried two disease-related variants, although there is no phase information. In another three of the 29 patients (10%) a single disease-related allele was identified. These patients were heterozygous for variants c.634C>T (p.R212C), c.4556C>G (p.T1519R), and c.6148G>C (p.V2050L), respectively. In the remaining 25 GPS[−] patients (86%) no disease-related allele was identified in the \textit{ABCA4} gene (Supplementary Table S5).

The STGD1 reference group included 14 patients, of whom two (G03-2346 and G03-3537) had three disease-related variants, seven had two disease-related variants, four (29%) revealed only one disease-related allele, and one revealed no disease-related alteration compared to the reference \textit{ABCA4} sequence (Supplementary Table S5).

Our data indicate a significant enrichment of disease-related monoallelic \textit{ABCA4} variants in GPS[+] over GPS[−] patients (56% vs. 10%, \( P = 0.0004 \)). In contrast, the occurrence of monoallelic \textit{ABCA4} variants in GPS[−] patients is not significantly different from the STGD1 patient group (10% vs. 29%, \( P = 0.19 \)). To test for regional founder effects that could affect the outcome of this study, we selected nine common coding variants in the \textit{ABCA4} gene with \( r^2 \leq 0.3 \), and compared the allele frequencies in 7,020 chromosomes from the NHLBI Exome Sequencing Project with patient groups GPS[+] (50 chromosomes), GPS[−] (58 chromosomes), and STGD1 (28 chromosomes). Eight of these markers showed no significant deviation of allele frequencies in the GPS[+], GPS[−], STGD1 groups when compared to the NHLBI data (\( P_{corr} > 0.5 \), Supplementary Table S6). In contrast, variant c.5603A>T (p.N1868I) was significantly enriched in GPS[+] and STGD1 patients, in agreement with previous findings that have led to the suggestion that the polymorphic variant c.5603A>T may act as a risk-increasing factor in \textit{ABCA4}-related pathology.\textsuperscript{37} Together, these data strongly suggest that there is no founder effect in the GPS[+] group as frequencies in the common sequence variants of the \textit{ABCA4} gene are not different from the GPS[+] group and the European-American NHLBI samples.

Our findings suggest that the excess of monoallelic disease-related variants could be causative of the GPS[+] phenotype. Consequently, the GPS[+] patient group should reveal a profile for the common known risk alleles at \textit{CFH} (rs1061170), \textit{ARMS2} (rs10490924), and \textit{C3} (rs2230199) that is similar for GPS[+], STGD1, and the ESP samples. Pooling of risk alleles increases statistical power and reveals significantly increased risk allele frequencies in GPS[−] compared to GPS[+] (\( P < 0.001 \)) while allele frequencies in GPS[+], STGD1 and the general population revealed no statistically significant differences (\( P > 0.5 \)).

![Figure 4](https://example.com/figure4.png)

**Figure 4.** Distribution of risk-increasing allele frequencies of \textit{CFH}: rs1061170:C, \textit{ARMS2}: rs10490924:T, and \textit{C3}: rs2230199:G in patients with GPS[+], GPS[−], STGD1, and 3,510 individuals with European descent from the NHLBI Exome Sequencing Project (ESP). The frequency of risk alleles is highest in the GPS[−] group for each of the risk alleles analyzed, and similar for GPS[+], STGD1, and the ESP samples. Pooling of risk alleles increases statistical power and reveals significantly increased risk allele frequencies in GPS[−] compared to GPS[+] (\( P < 0.001 \)) while allele frequencies in GPS[+], STGD1 and the general population revealed no statistically significant differences (\( P > 0.5 \)).
DISCUSSION

By FAF imaging we defined a rare GPS[+] subtype within the GA group of AMD patients that closely resembles STGD1, but that is distinct clinically from the autosomal recessive condition by a significantly later age of onset. In addition, we provided evidence that monoallelic disease-related ABCA4 variants are enriched greatly in this subgroup, while their genetic profile of risk-increasing alleles at the major AMD susceptibility loci is significantly different from the group of AMD patients and well comparable to the general population. Taken together, these findings suggested that the GPS[+] phenotype could be caused by genetic susceptibility conferred by distinct but rare mutant disease alleles in the ABCA4 gene rather than by the known common susceptibility alleles at loci, such as CFH, ARMS2, or C3.

Previous studies report controversial data on the contribution of mutant ABCA4 alleles to AMD pathophysiology. In light of the present findings, this could be explained partially by a random inclusion or exclusion of GPS[+] patients in the respective study group and would be true particularly if the spectrum of AMD cases in these studies focused mainly on patients with GA, exudative changes or a balanced mixture of these two most frequent late-stage outcomes. For example, the initial study by Allikmets et al. associated ABCA4 alterations mostly with the GA phenotype, where ABCA4 variants were found in 26 out of 134 patients. In contrast, only a single ABCA4 variant was identified in another 33 patients with exudative AMD. Our findings showed that GPS[+] patients carry significantly more mutant ABCA4 disease alleles (40%; 20 disease alleles/50 alleles analyzed) than GPS[−] patients (12%; 5/58, P = 0.0002, Fisher’s exact test, two-sided). Based on these data, the GPS[+] group stands out as a clinical subgroup within the AMD phenotype where individuals have an increased risk of suffering this condition likely due to ABCA4 predisposition. This is in full support with the findings by Allikmets et al. and suggests a role of rare ABCA4 variants in the etiology of a subset of AMD patients.

It should be noted, however, that disease-related ABCA4 variants may not explain fully the GPS[+] phenotype. Estimates predict a cumulative carrier frequency for ABCA4 variants as high as 1:20 in the general population. Assuming that the GPS[+] subgroup represents approximately 2% of GA-AMD, the latter being a common sub-phenotype of late stage AMD in possibly up to 4% of the general population, 2% of GA-AMD, the latter being a common sub-phenotype of late stage AMD in possibly up to 4% of the general population, this must be addressed in future sequencing studies. Our data provided support for a complex role of ABCA4 sequence variants in the etiology of AMD, specifically the FAF-defined GA phenotype termed GPS[+]. We showed that this infrequent subtype is associated significantly with monoallelic variants in ABCA4, arguing for a predisposing effect of such variants in a minor proportion of patients with AMD. In addition, our analysis of common variant frequencies in the ABCA4 gene showed that c.5603A>T (p.N1868I) is enriched greatly in the GPS[+] group, a variant that has been suggested previously to act as a risk-increasing factor in ABCA4-related pathology. Our findings were in accordance with the genotype-phenotype model suggested by Maugeri et al., proposing pathological effects dependent on a threshold of physiological ABCA4 activity. We, therefore, suggest that monoallelic carriers of ABCA4 variants have an increased risk for a late onset-macular degeneration that is diagnosed either as GPS[+] or eventually as atypical late onset STGD1. Although both diagnoses might reflect the same phenotype, attention should be paid to the counseling for recurrence risks. In the case of a monoallelic mode of action, an increased recurrence risk with reduced penetrance for first-degree relatives must be considered.

WEB RESOURCES


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lesions with markedly increased FAF signals outside the atrophic area as well as the area of atrophy itself. Clinical features that may allow differentiation relate to the peripapillary area. While almost all eyes with GPS[+] showed peripapillary atrophy, only 2% of patients with STGD1 have been described with peripapillary involvement. Typically, the peripapillary area is spared in retinal degeneration caused by ABCA4 variants. However, this must be addressed in future studies with larger cohorts.

Our study underscores the relevance of refined clinical phenotyping using novel imaging technologies to establish meaningful phenotype/genotype correlations in seemingly identical clinical manifestations. Furthermore, discrimination of phenotypes and their underlying genetic causes are important issues in future interventional clinical trials aimed at slowing the progression of GA in AMD. Patient selection for such trials must address the significant heterogeneity in the underlying pathogenic processes leading to the AMD condition.

We provided support for a complex role of ABCA4 sequence variants in the etiology of AMD, specifically the FAF-defined GA phenotype termed GPS[+]. We showed that this infrequent subtype is associated significantly with monoallelic variants in ABCA4, arguing for a predisposing effect of such variants in a minor proportion of patients with AMD. In addition, our analysis of common variant frequencies in the ABCA4 gene showed that c.5603A>T (p.N1868I) is enriched greatly in the GPS[+] group, a variant that has been suggested previously to act as a risk-increasing factor in ABCA4-related pathology. Our findings were in accordance with the genotype-phenotype model suggested by Maugeri et al., proposing pathological effects dependent on a threshold of physiological ABCA4 activity. We, therefore, suggest that monoallelic carriers of ABCA4 variants have an increased risk for a late onset-macular degeneration that is diagnosed either as GPS[+] or eventually as atypical late onset STGD1. Although both diagnoses might reflect the same phenotype, attention should be paid to the counseling for recurrence risks. In the case of a monoallelic mode of action, an increased recurrence risk with reduced penetrance for first-degree relatives must be considered.

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