Age-related Macular Degeneration

Clinical Features in a Large Family and Linkage to Chromosome 1q

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Objectives: To identify the chromosomal location of a disease-causing gene and to describe the clinical characteristics of a large family with age-related macular degeneration (ARMD).

Methods: An ARMD pedigree was identified, and the disease state of family members was documented by stereoscopic fundus photography and was classified using a modified version of the Wisconsin Age-Related Maculopathy Grading System. A genome-wide screen at approximately 6-centimorgan spacing using a DNA-pooling strategy combined with shared-segment analysis was used to identify likely chromosomal regions. The entire family was then screened at each likely locus, and 1 positive locus was refined by screening with markers at an average density of 0.5 centimorgan and subjected to parametric linkage analysis.

Results: In the 10 affected family members, ARMD was manifest by the presence of large, soft, confluent drusen accompanied by varying degrees of retinal pigment epithelial degeneration and/or geographic atrophy. Age-related macular degeneration segregated as an autosomal-dominant trait, with the disease locus mapping to chromosome 1q25-q31 between markers *D1S466* and *D1S413*, with a multipoint lod score of 3.00.

Conclusion: Age-related macular degeneration localized to chromosome 1q25-q31 (gene symbol, *ARMD1*) as a dominant trait in a large family with a predominantly dry phenotype.

Clinical Relevance: Identification of ARMD genes will facilitate early diagnosis and aid in understanding the molecular pathophysiological mechanisms of ARMD. This knowledge will contribute to the development of preventive and improved treatment strategies.

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AGE-RELATED macular degeneration (ARMD) is the leading cause of blindness in the United States and other western countries.[1-3] Approximately 7% of people 75 years and older have progressed to the late stage of this disease.[3] Although certain risk factors have been identified,[4-6] no interventions have been proven effective in preventing ARMD. Only laser photocoagulation has been established as an effective treatment, but its use is confined to a small proportion of patients with the exudative or wet form of ARMD, and its benefits are limited.[7-9] There is no treatment for the more common atrophic or dry form of ARMD.

Although the pathogenesis of ARMD remains unknown, there is growing evidence that genetic influences play an important role. Support for this view includes an increased family incidence of ARMD in affected individuals,[4,10-13] a strong concordance of ARMD in monozygotic twins,[14,15] and the results of segregation analysis suggesting the possibility of a single gene effect in a large proportion of patients.[16] Recently, mutations in the Stargardt disease gene (*ABCR*) at chromosome 1p21[17] were reported at a higher frequency in patients with ARMD compared with a control population.[18]

In this report, we describe a large family in which ARMD segregates as an autosomal-dominant trait that maps to chromosome 1q.

RESULTS

CLINICAL FINDINGS

Of the participating 21 family members at risk for ARMD (**Figure 1**), 10 were affected (**Table 1**). Blood samples were collected from an affected individual (patient 1009) who subsequently died before undergoing fundus photography. Her eyes, obtained postmortem, demonstrated pigment epithelium, photoreceptor, and choriocapillaris atrophy in the macula (**Figure 2**, A). These findings are consistent with the clinical diagnosis of geographic atrophy associated with a history of poor vision for several years before death.

PATIENTS AND METHODS

CLINICAL INFORMATION

Twenty-one individuals from a family with ARMD agreed to participate in the study, which was approved by the Institutional Review Board of Oregon Health Sciences University, Portland. For all but 1 individual, stereoscopic fundus photographs of the macula of both eyes were obtained. The remaining individual died before we obtained photographs, but the eyes were retrieved for histopathologic analysis. Clinical information, including visual acuity, was obtained for all affected individuals. In most instances, this information was obtained from the individual's local ophthalmologist or optometrist, and fundus photographs were taken at a local retina facility.

CLASSIFICATION OF ARMD

Stereoscopic fundus photographs of the macula were classified using a modified version of the Wisconsin Age-Related Maculopathy Grading System.[19] Each eye was classified independently by 3 ophthalmologists (M.L.K., A.E., and Robert C. Watzke, MD) without knowledge of the patient's genotype. Disagreements were adjudicated among the 3 graders. The patient's classification was based on the eye with the more advanced ARMD.

The following classification system was used: Group 1, definite ARMD is characterized by exudative ARMD (choroidal neovascularization, pigment epithelial detachment, or disciform macular scar) or geographic atrophy (area, >175 μm). Group 2, probable ARMD is characterized by the presence of large drusen (>125 μm) within 3000 μm of the fovea, with total cumulative drusen area exceeding 393 744 μm^2 (approximating the area within a 700-μm-diameter circle).[20] Nongeographic pigment atrophy and focal hyperpigmentation may or may not be present, and the features present in group 1 are absent. Group 3, probably no ARMD is characterized by large drusen present (>125 μm), but the cumulative area is less in extent than in group 2. Group 3 is characterized by the absence of exudative ARMD, geographic or nongeographic pigment atrophy, and focal hyperpigmentation. Group 4, no ARMD is characterized by no large drusen (>125 μm), geographic or nongeographic pigment atrophy, focal hyperpigmentation, or exudative maculopathy. Group 5, uncertain is characterized by absence of features seen in groups 1 and 2 and presence of any of the following: extensive small (<63 μm) or intermediate (63-125 μm) drusen, nongeographic pigment atrophy, or focal hyperpigmentation, or factors preventing reliable classification, such as media opacities, concomitant retinal disease, or pigment epithelial disturbance, with or without large drusen (>125 μm).

The definition of group 2 was based on findings[20] (Ronald Klein, MD, e-mail communication, November 18, 1997) demonstrating a 19-fold increase in the probability of developing late ARMD (group 1) for eyes with large drusen (>125 μm) and a minimum cumulative drusen area of 393 744 μm^2 (equivalent to an approximately 700-μm-diameter circle) located within 3000 μm of the fovea. Eyes classified as group 5, uncertain, are those in which accompanying conditions preclude accurate classification of ARMD or eyes that contain possible risk factors for the later development of late ARMD, including extensive small and intermediate drusen (<125 μm) or pigment epithelial abnormalities.

For purposes of linkage analysis, groups 1 and 2 were classified as affected and groups 3 and 4 were classified as unaffected. Those categorized as group 5 were classified as unknowns in the linkage analysis.

GENOTYPING

Genomic DNA was extracted from the blood of family members using a kit from Epicentre Technologies (Madison, Wis) according to their directions and was quantitated spectrophotometrically. Three pools of DNA were created. The first pool consisted of equimolar amounts of DNA from 8 affected family members (patients 1009, 2101, 1011, 1015, 1007, 2705, 1017, and 2005). The second pool was similarly derived from 4 unaffected family members (patients 2009, 2502, 2011, and 2103). These pools represented all affected and unaffected individuals who had been ascertained as the pooling was initiated. A third pool consisted of equimolar amounts of DNA from 8 unrelated individuals. Three affected cousins from the family with ARMD (patients 2101, 2705, and 2005) were also individually genotyped. Six hundred fifteen polymorphic microsatellite repeat markers at an average density of 6 centimorgans (cM) were used to genotype DNA from the 3 selected individuals and the 3 DNA pools. Five hundred seventy-two of these markers yielded clearly identifiable banding patterns. After the initial pooled genome-wide screen, markers from areas most suggestive of shared chromosomal segments were used to genotype all potentially informative family members. One region showing positive linkage was then mapped at an average marker density of 0.5 cM. Conditions for polymerase chain reaction, gel electrophoresis, blotting, and staining have been described previously.[21]

LINKAGE ANALYSIS

Two-point linkage between the disease locus and each microsatellite marker locus was tested by the parametric lod score method[22] using a computer program (MLINK).[23-25] Frequencies of the disease allele and of the normal alleles were assumed to be 0.001 and 0.999, respectively. Based on the pedigree in which there were 3 generations of affected individuals and male-to-male transmission, an autosomal-dominant mode of inheritance was assumed. Family members were placed in 1 of 5 age-related liability classes. Age-dependent penetrances for these classes were set to 0.001 (<50 years), 0.01 (50-54 years), 0.09 (55-64 years), 0.42 (65-74 years), and 0.95 (≥75 years). These values were determined from a set of 20 similar families with ARMD that we identified and are comparable with the prevalence observations reported in 3 studies based on approximately 15 000 individuals.[3,26,27] Allele frequencies reported by the Centre d'Etudes du Polymorphisme Humain (CEPH), Paris, France (http://www.cephb.fr/cephdb/), were used except for markers *D1S191, D1S202, D1S461, D1S492,* and *D1S412,* which were measured in a set of 92 unrelated individuals. Markers for multipoint linkage analysis, whose order was statistically supported, were identified using genotypes from CEPH pedigrees and the computer programs CRI-MAP[28] and MultiMap.[29] Multipoint linkage analysis was conducted using the VITESSE algorithm.[30]

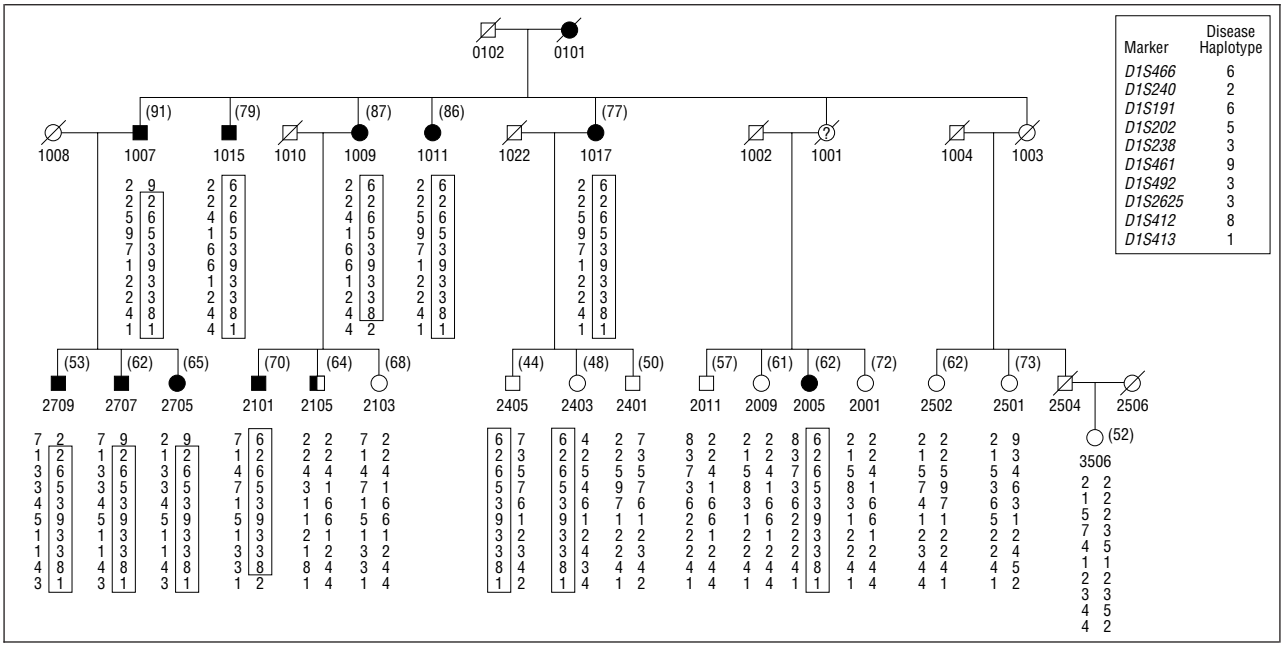

Figure 1. *Pedigree of the family with age-related macular degeneration. Black symbols indicate affected individuals; white symbols, unaffected individuals; squares, men; circles, women; slashes, the person is dead; question mark, the phenotype could not be determined; and half-filled symbol, the diagnosis was group 5, uncertain (see the "Patients and Methods" section for details). The numbers in parentheses represent the individuals' ages, and the numbers immediately beneath the symbols are the pedigree numbers. The 2 vertical columns of numbers show the haplotypes, with the disease-causing allele pattern boxed. The disease haplotype for each microsatellite marker is shown in the enclosed box (upper right-hand corner), with the marker numbers as indicated in the key.*

Table 1. Clinical Data of Affected Individuals*

Patient Pedigree No./Age, y	Age at Onset of Symptoms, y	Visual Acuity		Fundus Appearance	ARMD Group†
		OD	OS		
1007/91	71	CF	CF	Extensive GA	1
1009/87	71	NA	NA	Extensive GA (on histopathological examination)	1
1011/86	62	CF	CF	Extensive GA and large drusen	1
1015/79	None	20/25	20/30	Large confluent drusen, early GA	1
1017/77	75	20/50	20/50	Large confluent drusen, hyperpigmentation	2
2005/62	52	20/30	20/200	Large confluent drusen, nongeographic pigment atrophy, previous pigment epithelial detachments	1
2705/65	None	20/20	20/20	Large drusen, early GA	1
2707/62	60	20/40	20/100	Large confluent drusen, nongeographic pigment atrophy	2
2709/53	None	20/20	20/20	Large confluent drusen	2
2101/70	68	20/25	20/30	Large confluent drusen, nongeographic pigment atrophy	2

**CF indicates counting fingers; GA, geographic atrophy; NA, not available; and None, no symptoms experienced by patient.*

†Based on fundus photographs using the modified Wisconsin Age-Related Maculopathy Grading System for age-related macular degeneration (ARMD).[19] Grade 1 indicates definite ARMD; grade 2, probable ARMD.

For the remaining 9 affected members, the diagnosis was established by stereoscopic fundus photography. Four of these patients had geographic atrophy (Figure 2, B-E) and were classified as group 1, definite ARMD. One individual (patient 2005) had extensive large drusen and pigment changes and a photographically documented history of previous serous pigment epithelial detachments in both eyes and was thus also classified as group l (Figure 2, G). The remaining 4 individuals had extensive large, soft, confluent drusen in both eyes and were classified as group 2, probable ARMD (Figure 2, F and H-J). One of these individuals, a 70-year-old man (patient 2101), was thought by his local ophthalmologist to have had a pigment epithelial detachment in 1 eye. However, recent photographs (Figure 2, J) and results of fluorescein angiography were not conclusive for the presence of pigment epithelial detachment. Ten individuals were classified as unaffected (**Figure 3**, A and B); 7 of these patients were categorized as group 4, no ARMD (patients 2502, 2009, 3506, 2103, 2401, 2405, and 2001), and 3 were classified as group 3, probably no ARMD (patients 2011, 2403, and 2501). One individual (patient 2105) was classified as group 5, uncertain, because of the presence of pigmentary changes in the posterior pole of both eyes but without meeting the criteria for definite or probable ARMD.

The initial classification by the 3 independent graders was in agreement for 15 of the 20 individuals classified by fundus photography. For the remaining 5 individuals, initial classification by 1 of the graders differed

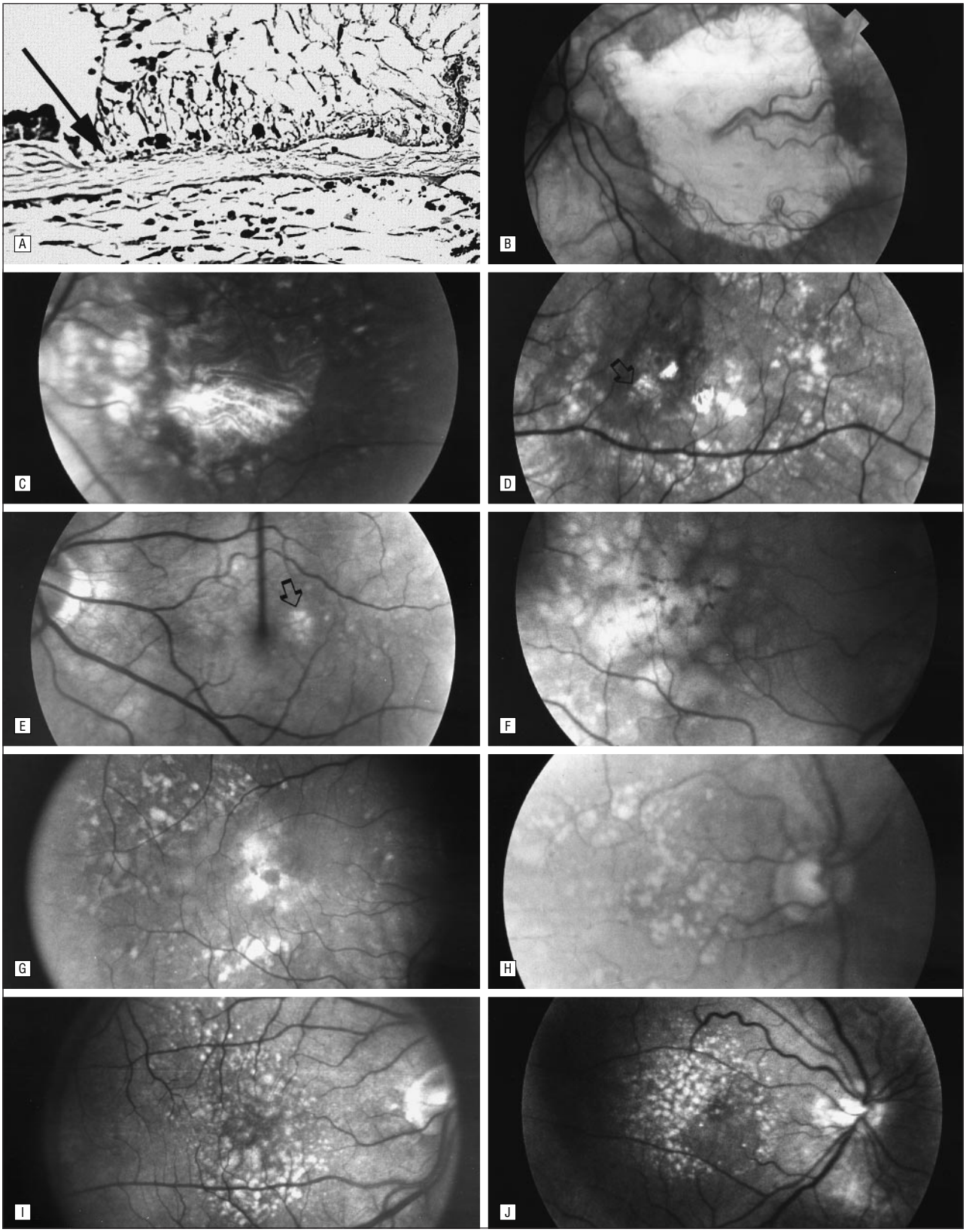

Figure 2. *Histopathologic and fundus photographs of affected family members. A, Histopathologic features of the right eye of patient 1009 (hematoxylin-eosin, original magnification × 200). The arrow indicates the transition between the relatively normal retinal pigment epithelium and the area of macular geographic atrophy demonstrating absence of retinal pigment epithelium, photoreceptors, and choriocapillaris. B, Left eye of a 91-year-old patient (1007). C, Left eye of an 86-year-old patient (1011). D, Left eye of a 79-year-old patient (1015). The arrow indicates an area of early geographic atrophy. E, Left eye of a 65-year-old patient (2075). The arrow indicates geographic atrophy. F, Right eye of a 75-year-old patient (1017). G, Right eye of a 62-year-old patient (2005). H, Right eye of a 62-year-old patient (2707). I, Right eye of a 53-year-old patient (2709). J, Right eye of 70-year-old patient (2101).*

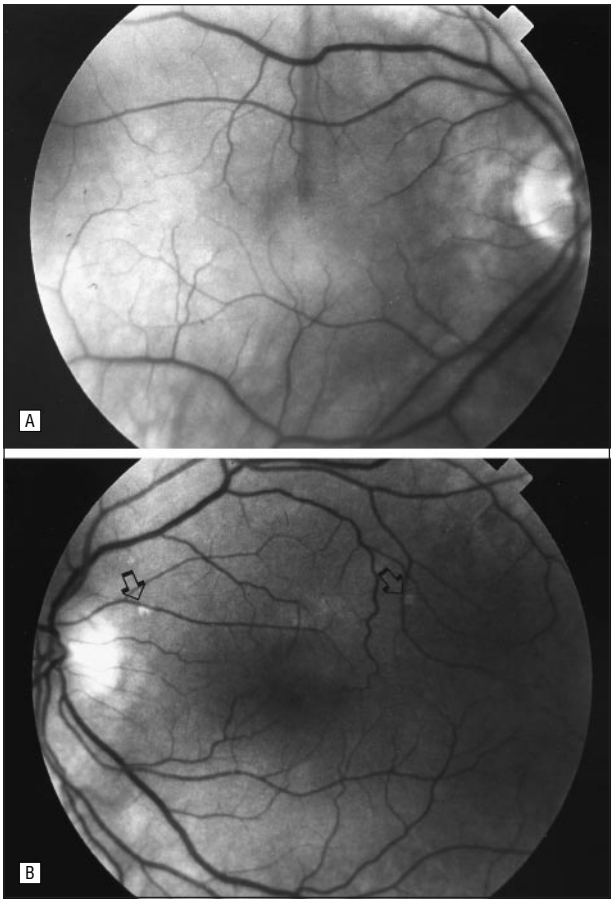

Figure 3. *Fundus photographs of selected unaffected family members. A, Right eye of a 62-year-old patient (2502; group 4, no age-related macular degeneration [ARMD]). B, Left eye of a 72-year-old patient (2501; group 3, probably no ARMD). The arrows indicate large drusen.*

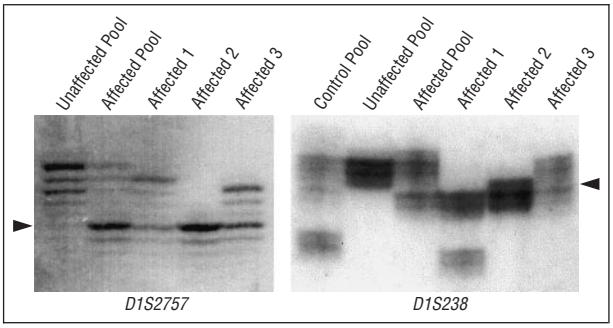

Figure 4. *Allele patterns for* D1S2757 *and* D1S238 *in the combined DNA pooling and shared-segment analysis. Lanes are a pool of unrelated control individuals, 4 unaffected individuals from the family, a pool of 8 affected individuals from the family, and 3 individuals from the family, as labeled. The arrowheads indicate the band of interest for each marker.*

Table 2. Two-Point lod Scores Between ARMD and Markers on Chromosome 1*

	lod Score†						
Marker	**0.00**	**0.01**	**0.05**	**0.10**	**0.20**	**0.30**	**0.40**
D1S466	−3.06	−1.00	0.14	0.50	0.58	0.38	0.12
D1S240	1.18	1.15	1.05	0.91	0.64	0.35	0.11
D1S191	2.68	2.63	2.41	2.13	1.54	0.90	0.28
D1S202	2.98	2.93	2.70	2.42	1.79	1.10	0.37
D1S238	1.78	1.74	1.58	1.38	0.95	0.53	0.15
D1S461	2.96	2.90	2.68	2.40	1.78	1.09	0.37
D1S492	2.79	2.73	2.52	2.25	1.66	1.00	0.33
D1S2625	1.59	1.55	1.40	1.21	0.84	0.48	0.16
D1S412	2.69	2.64	2.42	2.14	1.55	0.91	0.29
D1S413	−1.34	−0.19	0.35	0.48	0.42	0.23	0.06

**ARMD indicates age-related macular degeneration.*
†lod Scores given at θ values.

from that of the other 2 with regard to groups 3, 4, or 5. These differences were adjudicated to yield a final classification. For no individual family member was there any grader disagreement between affected (groups 1 and 2) and unaffected (groups 3 and 4) status.

Visual acuity for the 10 affected patients ranged from 20/20 to counting fingers. Age at diagnosis of ARMD ranged from 54 to 77 years (average, 65 years). For the 8 affected patients with visual symptoms, onset began between age 52 and 75 years (average, 67 years).

GENOTYPING

A high-density, genome-wide screen was performed on 6 DNA samples, 3 pools (unrelated, unaffected, and affected), and 3 affected individuals. The 3 individuals were cousins and were the 3 members of the family with ARMD who were separated by the greatest number of meioses. Of 572 microsatellite markers analyzed, 194 (33.9%) demonstrated a shared allele among the 3 cousins who were genotyped. In addition, each marker was scored for the preponderance of the shared allele in the affected pool and for its scarcity in the unaffected pools.[31-33]

The shared segments were reduced to 46 possible regions containing 2 or more adjacent markers. These regions were ranked and placed in 1 of 7 categories based on the scores of the DNA pools for their respective markers. Members of the pedigree who were used for pooling plus an additional 5 family members were then individually genotyped for linkage analysis, with markers in all 9 of the regions placed in the top category. Markers in 8 of the 9 regions yielded significantly negative lod scores (data not shown). Only 1 region contained markers (*D1S238* and *D1S2757*) that produced lod scores greater than 1.00. This was also the only region in the genome-wide screen in which an allele exhibited at least 50% of the total band intensity in the affected pool and was absent from the unaffected family pool in flanking markers (**Figure 4**).

LINKAGE ANALYSIS

Twenty-one individuals from the expanded pedigree were then genotyped at high density with 46 microsatellite markers from the Genethon map[34] that encompassed the region containing markers *D1S238* and *D1S2757*. The most informative markers, *D1S202* and *D1S461*, yielded maximum pairwise lod scores of 2.98 and 2.96, respectively, at $q = 0.00$ with the ARMD locus in this pedigree (**Table 2**). In total, 21 contiguous microsatellite markers between *D1S466* and *D1S2840* yielded positive lod scores (data not shown).

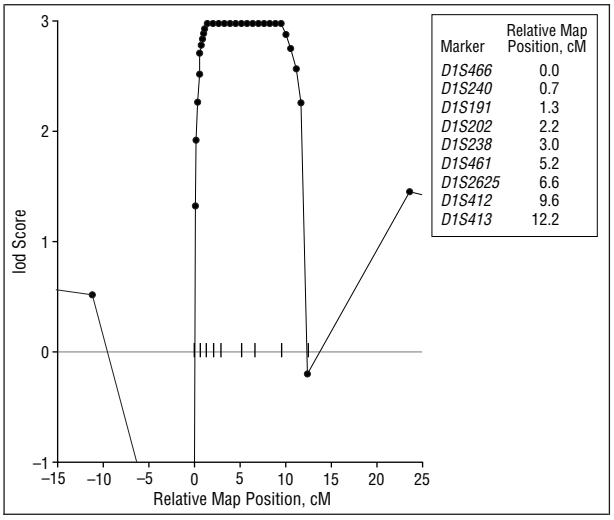

Figure 5. *Multipoint parametric lod scores obtained with the subset of 9 markers by overlapping 5-point analyses using VITESSE.[30] Plot shows lod scores plotted against relative chromosomal map position.*

Multipoint linkage analysis was performed between the disease gene and markers in this region on chromosome 1 using the program VITESSE.[30] A subset of the markers between *D1S466* and *D1S413,* whose local relative order was statistically well supported, was chosen for the analysis. Overlapping 5-point analyses were used to span the map of 9 markers. The maximum lod score was 2.98 (**Figure 5**), which is the same lod score obtained with *D1S202* in the 2-point analysis. Multipoint analysis with a phenocopy rate of 0.01 without age dependence, with a disease gene frequency of 0.038, or with both assumptions together yielded lod scores of 2.00, 2.35, and 1.70, respectively. A separate analysis using the age-dependent penetrance calculated from this single family rather than from 20 similar families yielded a multipoint lod score of 3.20. Based on recombinations in 2 individuals (patients 1007 and 1009), the interval of shared haplotypes was approximately 9 cM, defined by markers *D1S240* and *D1S412* (Figure 1).

Using 3 markers from the Stargardt disease gene locus (*ABCR*), we evaluated the possibility that this gene could be linked to ARMD in this family. All 3 markers across the locus yielded lod scores of less than −2.00, thus excluding this locus as a major gene effect in this family (**Table 3**).

Table 3. Two-Point lod Scores Between ARMD and Markers at the *ABCR* Locus*

	lod Score†						
Marker	**0.00**	**0.01**	**0.05**	**0.10**	**0.20**	**0.30**	**0.40**
D1S424	−3.30	−2.50	−1.40	−0.82	−0.28	−0.08	−0.02
D1S2804	−3.30	−2.50	−1.50	−0.84	−0.30	−0.09	−0.02
D1S236	−3.20	−3.10	−2.30	−1.60	−0.77	−0.30	−0.07

**ARMD indicates age-related macular degeneration.*
†*lod Scores given at θ value.*

COMMENT

Identification of ARMD pedigrees of sufficient size to allow direct linkage studies within 1 family has been difficult primarily because of its late age at onset, variable expressivity, and lack of reliable early diagnostic criteria.[13,35-39] Therefore, genetic investigation of ARMD has focused on nonparametric approaches using sibling pairs or small families[36] or candidate gene approaches based on macular dystrophies with earlier ages at onset.[17,18,37,39-44]

We identified a large ARMD pedigree that exhibits autosomal-dominant inheritance. Genetic analysis of this family produced significant evidence for linkage of the disease gene to a region of approximately 9 cM on chromosome 1q. The linkage model that we used is similar to that previously proposed by Gorin et al.[36]

Diagnostic classification of individuals with ARMD in this family was accomplished by using a scheme based on the well-established Wisconsin Age-Related Maculopathy Grading System.[19] Two individuals (patients 2405 and 2403) seem to be nonpenetrant, ie, they exhibit the disease haplotype but not the ARMD phenotype. They were the youngest family members analyzed, 44 and 48 years, and may manifest the disease at a later age. In this family, the average age at diagnosis of ARMD was 65 years, and the earliest age at onset of symptoms was 52 years.

Variability of fundus appearance among affected family members included amount and size of drusen, degree of drusen confluence, extent and severity of pigment epithelial atrophy, and presence of hyperpigmentation. However, there was considerable consistency in the phenotypic expression of ARMD within this family. In the sixth and seventh decades of life, clinical findings were predominantly characterized by the appearance of large, soft confluent drusen. In 1 individual (patient 2005), serous pigment epithelial detachments developed and subsequently spontaneously flattened, leaving nongeographic retinal pigment epithelial atrophy. In the seventh and eighth decades of life, large, confluent drusen with early geographic atrophy were accompanied by the onset of vision loss, whereas the 8th to 10th decades of life were characterized by fading of drusen, advanced geographic atrophy, and more severe central visual impairment. There was no definite evidence of choroidal neovascularization in any affected family members.

This predominantly dry ARMD phenotype is consistent with previous descriptions of geographic atrophy and large drusen.[45-48] Geographic atrophy is the most severe manifestation of dry age-related maculopathy, which has been reported to account for approximately 12% of legal blindness from ARMD.[1] In population-based studies, geographic atrophy has been found in approximately one third of eyes with late age-related maculopathy.[3,26,27]

Age-related macular degeneration is often thought to be inherited as a complex trait, with probable involvement of multiple genes and environmental factors.[17,35] However, dominant inheritance has been recognized in some familial cases.[10,12,36] Our findings suggest that at least a subset of ARMD is inherited as an autosomal-dominant trait.

We conclude that the disease-causing gene for ARMD (*ARMD1*) in this family is located within approximately a 9-cM region at chromosome 1q25-1q31, defined by microsatellite markers *D1S240* and *D1S412*. The localiza-

tion of this gene will allow early diagnosis of ARMD in this family. Identification of this and other genes linked to ARMD could lead to a better understanding of its pathophysiological mechanisms and could facilitate development of improved methods of prevention and treatment.

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REFERENCES

1. Ferris F. Senile macular degeneration: review of epidemiologic features. *Am J Epidemiol.* 1983;118:132-151.
2. Evans J, Wormald R. Is the incidence of registrable age-related macular degeneration increasing? *Br J Ophthalmol.* 1996;80:9-14.
3. Klein R, Klein BEK, Linton KLP. Prevalence of age-related maculopathy: the Beaver Dam Eye Study. *Ophthalmology.* 1992;99:933-943.
4. Hyman L, Lilienfield AM, Ferris FL, Fine SL. Senile macular degeneration: a case-control study. *Am J Epidemiol.* 1983;118:213-227.
5. Maguire MG. More pieces for the age-related macular degeneration puzzle. *Ophthalmology.* 1997;104:5-6.
6. The Eye Disease Case-Control Study Group. Risk factors for neovascular age-related macular degeneration. *Arch Ophthalmol.* 1992;110:1701-1708.
7. Macular Photocoagulation Study Group. Argon laser photocoagulation for senile macular degeneration: results of a randomized clinical trial. *Arch Ophthalmol.* 1982;100:912-918.
8. Macular Photocoagulation Study Group. Recurrent choroidal neovascularization after argon laser photocoagulation for neovascular maculopathy. *Arch Ophthalmol.* 1986;104:503-512.
9. Moisseiev J, Aljalel A, Masuri R, Treister G. The impact of the macular photocoagulation study results on the treatment of exudative age-related macular degeneration. *Arch Ophthalmol.* 1995;113:185-189.
10. Gass JDM. Drusen and disciform macular detachment and degeneration. *Arch Ophthalmol.* 1973;90:206-217.
11. Piguet B, Wells JA, Palmvang R, Chisholm IH, Bird AC. Age-related Bruch's membrane change: a clinical study of the relative role of heredity and environment. *Br J Ophthalmol.* 1993;77:400-403.
12. Silvestri G, Johnston PB, Hughes AE. Is genetic predisposition an important risk factor in age-related macular degeneration? *Eye.* 1994;8:564-568.
13. Seddon JM, Ajani UA, Mitchell BD. Familial aggregation of age-related maculopathy. *Am J Ophthalmol.* 1997;123:199-206.
14. Klein ML, Mauldin WM, Stoumbos VD. Heredity and age-related macular degeneration: observations in monozygotic twins. *Arch Ophthalmol.* 1994;112:932-937.
15. Meyers SM, Greene T, Gutman FA. A twin study of age-related macular degeneration. *Am J Ophthalmol.* 1995;120:757-766.
16. Heiba IM, Elston RC, Klein BEK, Klein R. Sibling correlations and segregation analysis of age-related maculopathy: the Beaver Dam Eye Study. *Genet Epidemiol.* 1994;11:51-67.
17. Allikmets R, Singh N, Sun H, et al. A photoreceptor cell-specific ATP-binding transporter gene (*ABCR*) is mutated in recessive Stargardt macular dystrophy. *Nat Genet.* 1997;15:236-245.
18. Allikmets R, Shroyer NF, Singh N, et al. Mutation of the Stargardt disease gene (*ABCR*) in age-related macular degeneration. *Science.* 1997;277:1805-1807.
19. Klein R, Davis MD, Magli YL, et al. The Wisconsin Age-Related Maculopathy Grading System. *Ophthalmology.* 1991;98:1128-1134.
20. Klein R, Klein BEK, Jensen SC, Meuer SM. The five-year incidence and progression of age-related maculopathy: the Beaver Dam Eye Study. *Ophthalmology.* 1997;104:7-21.
21. Wirtz MK, Samples JR, Kramer PL, et al. Mapping a gene for adult-onset primary open-angle glaucoma to chromosome 3q. *Am J Hum Genet.* 1997;60:296-304.
22. Morton NE. Sequential tests for the detection of linkage. *Am J Hum Genet.* 1955; 7:277-318.
23. Lathrop G, Laloel J, Julier C, Ott J. Strategies for multilocus linkage analysis in humans. *Proc Natl Acad Sci U S A.* 1984;81:3443-3446.
24. Ott J. *Analysis of Human Genetic Linkage.* Baltimore, Md: The Johns Hopkins University Press; 1991.
25. Terwilliger JD, Ott J. *Handbook of Human Genetic Linkage.* Baltimore, Md: The Johns Hopkins University Press; 1994.
26. Mitchell P, Smith W, Attebo K, Wang JJ. Prevalence of age-related maculopathy in Australia. *Ophthalmology.* 1995;102:1450-1460.
27. Vingerling JR, Dielemans I, Hofman A, et al. The prevalence of age-related maculopathy in the Rotterdam Study. *Ophthalmology.* 1995;102:205-210.
28. Lander ES, Green P. Construction of multilocus genetic maps in humans. *Proc Natl Acad Sci U S A.* 1987;84:2363-2367.
29. Matise TC, Perlin M, Chakravarti A. Automated construction of genetic linkage maps using an expert system (MultiMap): a human genome linkage map. *Nat Genet.* 1994;6:384-390.
30. O'Connell JR, Weeks DE. The VITESSE algorithm for rapid exact multilocus linkage analysis via genotype set-recording and fuzzy inheritance. *Nat Genet.* 1995; 11:402-408.
31. Sheffield VC, Pierpont ME, Nishimura D, et al. Identification of a complex congenital heart defect susceptibility locus by using DNA pooling and shared segment analysis. *Hum Mol Genet.* 1997;6:117-121.
32. Brugada R, Tapscott T, Czernuszewicz GZ, et al. Identification of a genetic locus for familial atrial fibrillation. *N Engl J Med.* 1997;336:905-911.
33. Carmi R, Rokhlina T, Kwitek-Black AE, et al. Use of a DNA pooling strategy to identify a human obesity syndrome locus on chromosome 15. *Hum Mol Genet.* 1995;4:9-13.
34. Dib C, Faure S, Fizames C, et al. A comprehensive genetic map of the human genome based on 5,264 microsatellites. *Nature.* 1996;380:iii-v.
35. Evans K, Bird AC. The genetics of complex ophthalmic disorders. *Br J Ophthalmol.* 1996;80:763-768.
36. Gorin MB, Sarneso C, Paul TO, Ngo J, Weeks DE. The genetics of age-related maculopathy. In: Hollyfield JG, Anderson RE, LaVail MM, eds. *Retinal Degenerations: Clinical and Laboratory Applications.* New York, NY: Plenum Press; 1993:35-47.
37. Stone EM, Sheffield VC. The molecular genetics approach to macular degeneration. In: Wright AF, Jay B, eds. *Molecular Genetics of Inherited Eye Disorders.* Chur, Switzerland: Harwood Academic; 1994:173-195.
38. De La Paz MA, Pericak-Vance MA, Haines JL, Seddon JM. Phenotypic heterogeneity in families with age-related macular degeneration. *Am J Ophthalmol.* 1997; 124:331-343.
39. Zhang K, Nguyen THE, Crandall A, Donoso LA. Genetic and molecular studies of macular dystrophies: recent developments. *Surv Ophthalmol.* 1995;40:51-61.
40. De La Paz MA, Pericak-Vance MA, Lennon F, Haines JL, Seddon JM. Exclusion of TIMP3 as a candidate locus in age-related macular degeneration. *Invest Ophthalmol Vis Sci.* 1997;38:1060-1065.
41. Gregory CY, Evans K, Wijesuriya SD, et al. The gene responsible for autosomal dominant Doyne's honeycomb retinal dystrophy (*DHRD*) maps to chromosome 2p16. *Hum Mol Genet.* 1996;5:1055-1059.
42. Weleber RG. Retinitis pigmentosa and allied disorders. In: Ogden TE, ed. *Basic Science and Inherited Retinal Disease.* Vol 1. 2nd ed. St Louis, Mo: Mosby; 1994: 335-466.
43. Weber BH, Vogt G, Pruett RC, Stohr H, Felbor U. Mutations in the tissue inhibitor of metalloproteinases-3 (TIMP3) in patients with Sorsby's fundus dystrophy. *Nat Genet.* 1994;8:352-356.
44. Weber BHF, Vogt G, Wolz W, Ives EJ, Ewing CC. Sorsby's fundus dystrophy is genetically linked to chromosome 22q13-qter. *Nat Genet.* 1994;7:158-161.
45. Sarks SH, Sarks JP. Age-related macular degeneration: atropic form. In: Schachat AP, Murphy RB, eds. *Medical Retina.* Vol 2. 2nd ed. St Louis, Mo: Mosby; 1994: 1071-1102.
46. Sarks JP, Sarks SH, Killingsworth MC. Evolution of geographic atrophy of the retinal pigment epithelium. *Eye.* 1988;1:552-577.
47. Maguire P, Vine AK. Geographic atrophy of the retinal pigment epithelium. *Am J Ophthalmol.* 1986;102:621-625.
48. Schatz H, McDonald HR. Atrophic macular degeneration: rate of spread of geographic atrophy and visual loss. *Ophthalmology.* 1989;96:1541-1551.