Age related macular degeneration in monozygotic twins and their spouses in Iceland

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ABSTRACT.

Purpose: **To examine the importance of genetic factors in age-related macular degeneration by using a twin study to compare the concordance of age-related macular degeneration in monozygotic twin pairs and their spouses.**

Methods: **This was a prospective study that included 50 twin pairs and 47 spouses. Zygosity was determined by genetic laboratory testing. Macular findings were graded based on the grading system used by the Macular Photocoagulation Study Group and the International ARM Epidemiological Study Group.**

Results: **The concordance of age-related macular degeneration was 90% in monozygotic twin pairs which significantly exceeded that of twin/spouse pairs (70.2%); p=0.0279. In the nine pairs that were concordant, fundus appearance and visual impairment were similar. Environmental factors and medical history were essentially the same in the twin pairs.**

Conclusion: **The statistically significant higher concordance of age-related macular degeneration in monozygotic twins compared to their spouses strongly suggests the importance of genetic factors.**

Key words: Age-related macular degeneration – macula – drusen – atrophy – monozygotic – concordance.

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Age-related macular degeneration is the most common cause of legal blindness among adults over the age of 50 years in Iceland (Björnsson 1982; Ólafsdóttir et al. 1992). It is also the most common cause of severe loss of central vision in individuals older than 65 years in the United States (Klein et al. 1992).

Although familial involvement has been recognized by several authors, the degree to which hereditary plays a role remains uncertain (Hyman et al. 1983; Klein et al. 1994, Meyers & Zachary 1988, Melrose et al. 1985; Meyers et al. 1995, De La Paz et al. 1997).

In classic twin research, the objective is to determine the heritability of a given trait. Since monozygotic twins are derived from the cleavage of a single fertilized ovum, they are assumed to be genetically identical. Dizygotic twins are no more genetically related than are other siblings from the same parentage. However, twins of either type are likely to share a similar physical and cultural environment until adolescence. Married couples are usually not genetically related and tend to share late-age and similar physical and cultural environments for a longer period of time. If the concordance rate in monozygotic twins approaches 100% and the rate in twins and their spouses who have been married for decades, is significantly less, then genetic transmission is suggested.

Potential risk factors for age-related macular degeneration have been described by Hyman et al. (1983) by using case-control and population-based studies. These associated risk factors include light skin and iris color, hyperopia, a positive family history as well as several systemic and environmental factors.

To further explore the importance of genetic and environmental factors for age-related macular degeneration in Iceland we examined a large number of monozygotic twins along with their spouses.

Methods

The study was approved by the University of Iceland Joint Committee on Clinical Investigations and was conducted in accordance with the Declaration of Helsinki of the World Medical Association regarding scientific research on human subjects.

Through the Icelandic twin registry and the national census, all twins of the same gender over the age of 55 were identified.

The twin cohort material was used to determine genetic and environmental effects in age-related macular degeneration. All twin pairs in the cohort born before 1930 with both members alive were contacted by telephone to determine zygosity. Self-reported dizygotic twins were excluded from entry into the study. Twins claiming to be identical were assumed to be monozygotic and recruited for the study. Monozygosity was confirmed through analysis of genetic markers (histocompatibility antigens and red blood cell polymorphism). Out of a total

Table 1. Agreement between monozygotic twin pairs for the presence or absence of age-related macular degeneration.

		Twin	One	
		N	Y	Total
Twin	N	36	4	40
Two	Y	1	9	10
	Total	37	13	50

Twin-Pairs agreement: 45/50 (90%).
Twin-Pairs concordance: 9/50 (18%).

Table 2. Agreement between monozygotic twin/spouse pairs for the presence or absence of age-related macular degeneration.

		Twin		
		N	Y	Total
Spouse	N	31	9	40
	Y	5	2	7
	Total	36	11	47

Twin/Spouse agreement: 33/47 (70.2%).
Twin/Spouse concordance: 2/47 (4.3%).

of 183 pairs, 50 twin pairs were monozygotic with both members alive and available for an eye exam. Therefore, these 50 twin pairs qualified for entry and were examined along with 47 spouses.

Clinical evaluation included ocular and medical histories, visual acuity, cycloplegic autorefraction, Goldmann applanation tonometry, and slitlamp examination. Iris pigmentation was documented and classified as lightly pigmented (grey or blue), medium pigmented (hazel brown) or dark (dark brown). Direct and indirect ophthalmoscopy were performed as well as fundus photographs taken. All examinations and measurements were performed by Dr. Sverrisson, Dr. Stefansson and Dr. Gottfredsdottir who all used the same equipment. Age-related macular degeneration was classified into exudative and nonexudative. The nonexudative form featured drusen and abnormalities of the retinal pigment epithelium. Drusen were graded by size and type (Bird et al. 1995; Macular Photocoagulation Study Group 1982) Small drusen were less than 63 μm in diameter, intermediate drusen between 63 and125 μm and large drusen greater than 125 μm. Drusen with fuzzy or ill-defined borders were classified as soft, and two or more drusen with touching borders were said to be confluent. The exudative form included any exudative changes (hemorrhage, exudate, serous retinal detachment, serous or hemorrhagic retinal pigment epithelial detachment, or a disciform scar) within 3.0 mm of the center of the fovea. Exudative changes or geographic atrophy involving most of the fovea were also referred to as severe or advanced age-related macular degeneration. Drusen and retinal pigment epithelial degeneration were referred to as mild or early age-related macular degeneration. These criteria are consistent with previous clinical classifications and clinicopathologic correlation by other investigators (Klein et al. 1991; Klein et al. 1992; Bressler et al. 1990).

Results

One hundred monozygotic twins (50 pairs) along with 47 spouses were included in the study. All participants were Caucasians. There were 26 female twin pairs and 24 male twin pairs.

The age of the twins ranged from 63 to 84 years with a mean of 67 years and the spouses ranged in age from 48 to 81 years with a mean of 64 years. The difference in mean age between twins and spouses was not statistically significant, nor was it considered substantial enough to adjust for in the analysis of concordance. Mean time of marriage was 30 years (range 26–50). Agreement for age-related macular degeneration was 90% (9 of 14) which significantly exceeded that of twin/spouse pairs, 70% ($p=0.0279$, Chi-square test). Concordance for AMD among twin pairs was 18% (9/50), which significantly exceeded concordance among twin/spouse pairs, which was 4.3% (2/47), using the two-tailed Fisher's exact test ($p=0.05$). Two twin/spouse pairs were concordant and five twin pairs were disconcordant

Table 3. Clinical characteristics for monozygotic twin pairs concordant for age-related macular degeneration.

Twin		Right Eye				Left Eye			
pair	Sex/Age	Visual Acuity	Refractive error	Iris color	Retina	Visual Acuity	Refractive error	Iris color	Retina
1-A_1	M/64	20/30	+1.25	light	HD, PC	20/40	+2.00	light	HD, PC
1-A_2	M/64	20/30	+1.50	light	HD, PC	20/30	+1.25	light	HD, PC
2-A_1	M/75	20/60	−0.25	medium	HD, PC, A	20/60	−0.25	medium	HD, PC, A
2-A_2	M/75	20/50	+0.50	medium	HD, PC	20/20	+0.75	medium	Normal
3-A_1	F/83	20/200	−0.75	light	SD	20/50	−0.25	light	SD
3-A_2	F/83	20/60	+0.75	light	SD	20/60	+1.00	light	SD
4-A_1	F/77	20/50	plano	light	HD, PC, A	20/50	plano	light	HD, PC, A
4-A_2	F/77	20/50	−0.25	light	HD, PC	20/50	plano	light	HD, PC
5-A_1	F/77	20/200	+1.00	light	CD	20/80	+1.00	light	CD
5-A_2	F/77	20/50	+2.50	light	CD	20/60	+3.00	light	CD
6-A_1	M/71	20/70	+1.50	medium	SD	20/25	+1.25	medium	SD
6-A_2	M/71	20/60	+1.50	medium	SD	20/30	+1.25	medium	SD
7-A_1	M/71	20/40	+0.75	light	CD	20/40	+0.50	light	CD
7-A_2	M71	20/30	+0.75	light	CD	20/30	+0.75	light	HD, PC, A
8-A_1	M/72	20/80	−0.50	medium	HD, PC, A	20/70	−0.75	medium	HD, PC, A
8-A_2	M/72	20/50	−0.25	medium	HD, PC, A	20/30	+0.25	medium	Normal
9-A_1	M/73	20/30	−0.25	dark	HD, PC	20/30	+0.25	dark	HD, PC
9-A_2	M/73	20/60	+0.25	dark	SD	20/70	+0.50	dark	SD

F=female, M=male, HD=hard drusen, SD=soft drusen, CD=confluent drusen, PC=pigmentary changes, A=atrophy.

for age-related macular degeneration (Table 1 and 2). Seven of the nine concordant twin pairs had macular degeneration in both eyes. All of the twins and all except for one spouse had the nonexudative form of the disease. There were 12 men and 6 women in the concordant twin group. The average age for affected twins was 72 years compared to 66 years for affected spouses. The average age for concordant twins was 73 years compared to 69 years for disconcordant twin pairs. Five of the nine concordant twin pairs had light (grey or blue) pigmented irises, three had medium (hazel) pigmented irises and one pair had dark irises (dark brown).

Two twin pairs were concordant for both age-related macular degeneration and glaucoma. Of these two twin pairs, one pair had pseudoexfoliation glaucoma. There was a high correlation in refractive error in the twin group, however, there was no correlation found in the twin/spouse group. Mean refractive error in the twin group concordant for age-related macular degeneration was plus 1.25 D in the right eye and plus 1.14 for the left eye. In the disconcordant group, the mean refractive error was plus 0.97 D in the right eye and plus 0.92 for the left eye. Mean refractive error in the whole twin group was plus 1.00 D for right eye and plus 1.00 D for left eye. This difference was not statistically significant. Clinical characteristics for twin pairs concordant for age-related macular degeneration are shown in Table 3. We did not identify any environmental risk factors for age-related macular degeneration from the occupational, residential or medical histories of the twins.

Discussion

The purpose of the study was to determine the importance of genetic and environmental factors in age-related macular degeneration by using a twin study to compare the concordance in monozygotic twins and their spouses. This population has not been studied previously in Iceland. The approach in this study differs from classical twin studies wherein concordance is contrasted between monozygotic and dizygotic twins. However, siblings often do not share the same environment except during childhood. In the current study data for spouses were collected as a control for late-age shared environment.

It is well established that heredity plays a major role in the development of drusen-related macular degeneration with early age onset, known as familial or dominantly inherited drusen (Deutman & Jansen 1970; Gass 1973). Some investigators believe that dominantly inherited drusen are distinct from drusen occurring later in life (Deutman & Jansen 1970), but others (Gass 1973) have concluded that macular changes seen in patients with dominant drusen are identical to those seen in older patients with age-related macular degeneration.

Several studies have observed concordance of age-related macular degeneration and drusen in monozygotic twin pairs (Meyers et al. 1995; Klein et al. 1994; Meyers & Zachary 1988; Melrose et al. 1985). Our results are in agreement with these studies. However, all the twin pairs in the present study had nonexudative age-related macular degeneration. Some studies suggest that large soft drusen and pigment epithelial changes are risk factors for the development of more severe maculopathy (Smiddy & Fine 1984; Bressler et al. 1990). We observed two twin pairs with soft drusen bilaterally, one pair with confluent drusen bilaterally, and one pair where one of the two twins had confluent drusen bilaterally and the other twin had confluent drusen in one eye but hard drusen and pigmentary changes and atrophy in the other eye. Since large drusen may be part of the disease process for severe age-related macular degeneration these individuals should be closely followed for evidence of progression (De La Paz et al. 1997). The five twin pairs who were disconcordant for the disease were significantly younger than concordant pairs. These pairs may become concordant in the future. However, the eyes of these patients may be undergoing normal aging, as described in histopathologic studies (Green et al. 1985; Sarks 1982). Some of these eyes may develop age-related macular degeneration, but currently we cannot identify which ones will do so.

Volunteer bias in twin studies may result in the overrepresentation of monozygotic twin pairs and of women because women are more likely than men to participate in research projects (Lykken et al. 1978). We did not find this in present study. There was no difference between genders in participation or in twins affected.

Although the pathogenesis for age-related macular degeneration is unknown, several studies have associated familial, ocular and systemic risk factors with macular degeneration (Leibowitz et al. 1980; Klein & Klein 1993; Hyman et al. 1983; Blumenkranz et al. 1986). Among previously identified risk factors are light skin and iris color (Hyman et al. 1983). All participants in the present study were Caucasians, however, there was no correlation between iris pigmentation and age-related macular degeneration: five pairs had light pigmented irises, three had medium pigmentation, and one pair had dark irises. Hyperopia has been identified as one of the risk factors for age-related macular degeneration (Hyman et al. 1983), but we did not find this in our study. There was no association between refractive error and macular degeneration and there was no statistically significant difference in refraction between twins with and without macular degeneration.

The statistically significant higher concordance of age-related macular degeneration in monozygotic twin pairs compared to twin/spouse pairs suggests the importance of genetic factors in age-related macular degeneration. The magnitude of this genetic component and the mode of inheritance cannot be determined from this study. However, twin studies provide a unique and particularly valuable way to determine whether a genetic predisposition exists and can lead to more detailed genetic or epidemiologic studies.

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