Heritability of Cilioretinal Arteries: A Twin Study

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Purpose. To determine whether the presence of one or more cilioretinal arteries, a distinct element of the pattern of fundus vessels, is genetically programmed, influenced by environmental factors, or the result of random mechanisms of vascular development.

Methods. The fundi of 112 pairs of healthy monozygotic and dizygotic twins were examined using digital fundus photography and visual assessment of grayscale fundus photographs and color transparencies to detect the presence of cilioretinal arteries.

Results. Cilioretinal arteries were present in 45.1% of participants and 28.8% of eyes. The majority of cilioretinal arteries, 88.2%, were located temporally, and 11.8% were located nasally. Monozygotic twins had higher concordance rates for cilioretinal arteries than dizygotic twins. Tetrachoric correlations and Mantel-Haenszel odds ratios demonstrated statistically significant evidence of a genetic effect underlying the presence of cilioretinal arteries ($P < 0.01$). Statistical analysis supported the hypothesis that additive genetic factors influenced the presence of cilioretinal arteries with a heritability of 71.4%, the remaining variance being attributable to nonshared or random environmental factors.

Conclusions. The presence or absence of one or more cilioretinal arteries in healthy persons is markedly influenced by genetic factors. (*Invest Ophthalmol Vis Sci.* 2005;46:3850–3854) DOI:10.1167/iovs.05-0177

Some vascular diseases in humans appear to be linked to the pattern of distribution of retinal blood vessels. Knowing whether a variation in the distribution of retinal vessels is attributable to genetic or environmental factors may facilitate elucidation of the pathogenesis of disease in the human retina. Consequently, retinal vascular patterns and the mechanisms whereby they are laid out are of fundamental interest for clinical ophthalmology. In primates, including humans, the inner retina is supplied primarily or exclusively by the central retinal branch of the ophthalmic artery. Occasionally the central retinal artery is assisted by one or more cilioretinal arteries. These arteries are derived directly from the circle of Zinn, which is formed by small branches from the short posterior ciliary arteries, which also supply the choroid. It is of clinical relevance that a temporal cilioretinal artery supplying the fovea may spare the fovea in case of central retinal artery occlusion.[1] Furthermore, patients with advanced high-tension open-angle glaucoma have better preservation of the central visual field and visual acuity in the presence of a temporal cilioretinal artery, presumably because it is associated with a better blood supply to the prelaminar portion of the optic disc.[2] In addition, the vascular layout of the retina may influence the pattern of distribution of diabetic retinopathy and branch retinal vein occlusion.[3]

The prevalence of one or more cilioretinal arteries has previously been reported to be 49.5% of individuals and 32.1% of eyes, based on a review of stereo fundus photographs and fluorescein angiograms from 1000 healthy persons.[4] Using direct ophthalmoscopy, another study found a cilioretinal artery prevalence of 26% of individuals in a population of 172 healthy persons.[5] In the present study, we examined fundus photographs of 112 pairs of healthy twins (224 persons, 448 eyes) to assess the relative influence of genetic and environmental factors on the presence of cilioretinal arteries.

Methods

Subjects and Protocol

We examined 59 monozygotic (MZ) and 55 dizygotic (DZ) same-sex twin pairs, aged 20 to 46 years. The persons were recruited from a population-based register comprising twins born in Denmark between 1870 and 1996 (The Danish Twin Registry, University of Southern Denmark, Odense, Denmark).[6] Only subjects in self-assessed good health were invited to participate. Exclusion criteria for twin pairs were unclear refractive media, manifest eye disease, or fundus photographs of unacceptable quality in either member of the pair. One MZ and one DZ twin pair did not want to have their fundus photographs taken. A total of 58 MZ and 54 DZ twin pairs were included in the present study, and all fundus photographs were of good quality. Zygosity was determined by means of genetic markers, using nine microsatellite and restriction fragment length polymorphism markers. The study was approved by the Medical Ethics Committee of Copenhagen County and followed the tenets of the Helsinki Declaration, including informed consent. All persons underwent an ophthalmological examination including refraction, visual acuity determination, slit-lamp biomicroscopy, and fundus photography after pupil dilation (using 10% phenylephrine hydrochloride and 1% tropicamide) and a clinical examination including an oral glucose tolerance test and blood pressure measurement. Digital grayscale fundus photographs (20° and 50°, 1024 × 1024 pixels) were recorded in red-free illumination (filter: Wratten 54; Eastman Kodak, Inc., Rochester, NY) using a retinal camera (model TRC-50X; Topcon Corp., Tokyo, Japan). The study design and photography protocol were as described by Kessel et al.[7] and Hougaard et al.,[8] who conducted studies on the heritability of lens aging (autofluorescence) and retinal nerve fiber layer thickness in the present twin population.[7,8]

Two independent observers evaluated the digital red-free grayscale fundus photographs to assess the presence, number, and location of

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Supported by the Danish Eye Health Society; The Danish Association of the Blind; Center for Biomedical Optics and New Laser Systems (BIOP) Graduate School; The Danish Research Agency; and a Research Career Award (Grant 8–2002-130) from the Juvenile Diabetes Research Foundation (ML).

Submitted for publication February 10, 2005; revised May 27, 2005; accepted August 19, 2005.

Disclosure: **N.C.B.B. Taarnhøj**, None; **I.C. Munch**, None; **K.O. Kyvik**, None; **B. Sander**, None; **L. Kessel**, None; **T.I.A. Sørensen**, None; **J.L. Hougaard**, None; **M. Larsen**, None

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TABLE 1. Clinical Characteristics and Cilioretinal Artery Phenotype of Study Participants

Characteristic or Phenotype	MZ Twins (n = 116)	DZ Twins (n = 108)	P-Value
Pairs	58	54	
Subjects	116	108	
Eyes	232	216	
Female/male subjects	62/54	64/44	
Age* (years)	34.9 ± 7.5	35.0 ± 7.2	0.93†
Arterial blood pressure* (mm Hg)	85.3 ± 10.0	86.3 ± 8.6	0.42†
Cilioretinal artery phenotype			
Any eye (both eyes + one eye only)	52	49	0.94‡
Both eyes	15	13	0.84‡
One eye only (left eye only + right eye only)	37	36	0.82‡
Right eye only	19	21	0.55‡
Left eye only	18	15	0.73‡
Proportion of eyes with cilioretinal arteries, any location	67/232	62/216	0.97‡

* Values are means ± SD.
† Two-tailed t-test.
‡ Hypothesis test of proportions.

cilioretinal arteries. A cilioretinal artery was defined as a retinal arterial branch noncontiguous with the central retinal artery, coursing through a near-180° hook as it emerges from underneath the retinal pigment epithelium at the rim of the optic disc. The location of a cilioretinal artery was classified as temporal or nasal with respect to the center of the optic disc. Discrepant classifications underwent independent arbitration by a third investigator, who decided the classification, using color transparencies when needed.

Statistics

The differences in sex, age, and blood pressure in persons with one or more cilioretinal arteries compared to persons with no cilioretinal arteries were assessed by χ^2 tests and two-sided t-tests. We performed a test of proportions to compare the phenotype proportions for MZ and DZ twin pairs. Test significance was evaluated at the 5% level.

We compared MZ and DZ twin pairs by means of probandwise concordance rates, Mantel-Haenszel odds ratios, and tetrachoric correlations, as described elsewhere.[9–11] Probandwise concordance rates estimate the risk of having a certain phenotype, given that one's twin partner has this phenotype. The odds ratio estimates the increased risk of having a certain phenotype given that one's twin partner has the phenotype, compared to the risk if one's twin partner does not have the phenotype. The Mantel-Haenszel weighted odds ratio tests the difference between the odds ratios for MZ pairs and DZ pairs, using computer software (Epi Info; available at http://www.cdc.gov/epiinfo).[12] A statistically significant Mantel-Haenszel test provides evidence for a genetic influence on the phenotype.

Tetrachoric correlations, as well as estimation of heritability and best-fitting etiological model by means of structural equation modeling, were carried out using computer software (MX; Michael C. Neale, Department of Psychiatry, Virginia Commonwealth University; available at www.vcu.edu/mx/).[13] These calculations are based on a liability model, which assumes that the dichotomous distribution of cilioretinal arteries (present versus not present) reflects an underlying normally distributed liability of the population. When a threshold value of the liability is exceeded, an individual is affected, otherwise not. The threshold reflects the prevalence of the trait. These are standard assumptions in quantitative genetic analysis of categorical traits.[14] The classical twin model is based on the assumption that MZ twin pairs share all their genes, while DZ twin pairs, like other siblings, share on average 50% of their genes, and that both MZ and DZ twin pairs share a common environment to the same extent. This means that a greater similarity among MZ than among DZ twin partners for a certain phenotype can be due only to genetic factors.[15] Structural equation modeling quantifies sources of individual variation by decomposing the observed phenotypic variance into genetic and environmental variance. The genetic contribution can be further divided into an additive (A) genetic variance component (representing the influence of alleles at multiple loci acting in an additive manner) and a nonadditive (D) genetic variance component (representing intralocus interaction [dominance] and interlocus interaction [epistatis] of alleles). The environmental component is subdivided into a common (C) environmental variance component (representing environmental factors affecting both twins in a pair, a source of similarity) and a nonshared or random

TABLE 2. Probandwise Concordance Rates for the Presence and Location of Cilioretinal Arteries in Study Participants*

	MZ Twins			DZ Twins		
Cilioretinal Artery Location	Probands in Concordant Pairs	Probands in Discordant Pairs	Concordance Rate [% (95% CI)]	Probands in Concordant Pairs	Probands in Discordant Pairs	Concordance Rate [% (95% CI)]
Right eye	22	12	64.7 (46.0–83.4)	16	18	47.1 (26.3–67.8)
Left eye	18	15	54.5 (34.1–75.0)	10	18	35.7 (13.0–58.5)
Any eye	38	14	73.1 (59.5–86.7)	28	21	57.1 (40.6–73.7)
One eye	20	17	54.1 (34.7–73.5)	14	22	38.9 (18.7–59.1)
Both eyes	8	7	53.3 (22.8–83.9)	4	9	30.8 (−1.9–63.4)

* A proband is the person in a twin pair that has one or more cilioretinal arterioles. In concordant pairs both twins are affected; in discordant pairs only one twin is affected. Concordance rate is calculated as the number of probands in concordant pairs divided by the sum of probands in concordant and discordant pairs.

(*E*) environmental variance component (representing environmental factors not shared by twins, a source of dissimilarity). The latter component (*E*) also includes random factors and measurement errors.[16] Heritability is defined as the proportion of the total phenotypic variance attributable to genetic variance. The components *C* and *D* cannot be estimated simultaneously in a twin study. We fitted the *ACE* and *ADE* models and the submodels *AE*, *CE*, and *E* to the data. The criteria for best-fitting model were based on Akaike's information criterion (AIC), goodness-of-fit χ^2 test, degrees of freedom, and *P*-value. The model with the lowest negative AIC reflects the best balance between goodness of fit and parsimony.

The phenotype *any eye* means that a person has one or more cilioretinal arteries in one eye or in two (both) eyes, meaning that a person is affected by any kind of cilioretinal artery. The phenotype *both eyes* denotes a person with one or more cilioretinal arteries in each eye. *Any location* denotes the presence of a cilioretinal artery at any location—nasal, temporal, or both.

In this study, ascertainment is independent of affection status in that all twin pairs were enrolled in the study and then examined to asses the prevalence of cilioretinal arteries. A proband is the affected part in a twin pair. In discordant twin pairs there is one proband, and in concordant twin pairs there are two probands.

Results

The per-person prevalence of cilioretinal arteries, i.e., the presence of one or more cilioretinal arteries in either of a subject's two eyes, was 45.1% (95% confidence interval [CI]: 38.6%–51.6%), 101 participants in a study population of 224. In MZ twins, the per-person prevalence of one or more cilioretinal arteries was 44.8% (95% CI: 35.8%–53.9%), and among DZ twins it was 45.4% (95% CI: 36.0%–54.8%). The per-eye prevalence of cilioretinal arteries, i.e., the presence of one or more cilioretinal arteries in a given eye, was 28.8% (95% CI: 24.6%–33.0%; $n = 448$) for the entire study population, being 28.9% (95% CI: 23.0%–34.7%) in MZ twins and 28.7% (95% CI: 22.7%–34.7%) in DZ twins. Of the total number of cilioretinal arteries, 88.2% (95% CI: 82.8%–93.7%) were located temporally and 11.8% (95% CI: 6.3%–17.2%) were located nasally. The per-person prevalence of cilioretinal arteries was 49.0% (95% CI: 39.1%–58.9%) in men and 42.1% (95% CI: 33.4%–50.7%) in women. There was no impact of sex (χ^2, $P = 0.30$), age (*t*-test, $P = 0.29$), or mean arterial blood pressure ($P = 0.76$) on the presence of cilioretinal arteries. Clinical characteristics and cilioretinal phenotypes of the participants are described in Table 1; there was no significant difference in the proportions (prevalence) of phenotypes between MZ and DZ twins.

Probandwise concordance rates for cilioretinal artery phenotypes were consistently higher in MZ twins than in DZ twins for all phenotypes, but the difference did not reach statistical significance for any single phenotype (Table 2).

Odds ratios were significantly higher for MZ twins than for DZ twins for all phenotypes when using the Mantel-Haenszel weighted odds ratio test for zygosity (Table 3). The odds ratio results agreed with the tetrachoric correlations, where there was a significantly higher correlation in MZ than in DZ twins for all phenotypes (Table 3).

Tetrachoric correlations and structural equation modeling of the phenotypes *both eyes* (Table 4)*, one eye only, any eye, right eye, right eye only, left eye, and left eye only* (Supplementary Tables, http://www.iovs.org/cgi/content/full/46/10/3850/DC1) support that an *AE* model comprising additive genetic effects and random environmental effects was the best-fitting liability model and most aptly describes all phenotypes. In *both eyes, one eye only, any eye, left eye only,* and *right eye,* 71% to 74% of the phenotypic variance

Table 3. Tetrachoric Correlations and Zygosity-Specific Mantel-Haenszel Odds Ratios for the Cilioretinal Artery Phenotypes

Cilioretinal Artery, Any Location*	Concordant Pairs		Discordant Pairs		Nonaffected Pairs		Tetrachoric Correlation [TC (95% CI)]		Odds Ratio† [OR (95% CI)]		Mantel-Haenszel Weighted OR‡
	MZ	DZ	MZ	DZ	MZ	DZ	MZ	DZ	MZ	DZ	
Both eyes	4	2	7	9	47	43	0.74 (0.29–0.94)	0.43 (−0.18–0.83)	15.7 (2.0–148.4)	4.3 (0.41–41.6)	8.37 ($P = 0.001$)
One eye only	10	7	12	17	36	30	0.71 (0.36–0.90)	0.38 (−0.07–0.72)	10.0 (2.2–48.4)	2.9 (0.7–12.4)	5.17 ($P < 0.001$)
Any eye	19	14	14	21	25	19	0.72 (0.41–0.90)	0.33 (−0.08–0.67)	9.7 (2.5–39.8)	2.4 (0.7–8.5)	4.55 ($P < 0.01$)
Right eye	11	8	12	18	35	28	0.73 (0.39–0.91)	0.37 (−0.07–0.71)	11.0 (2.5–52.4)	2.8 (0.7–11.1)	5.09 ($P < 0.001$)
Left eye	9	5	15	18	34	31	0.57 (0.17–0.83)	0.23 (−0.24–0.63)	5.5 (1.3–23.4)	1.9 (0.4–8.7)	3.3 ($P = 0.01$)
Right eye only	4	2	5	10	49	42	0.84 (0.44–0.98)	0.37 (−0.23–0.79)	32.7 (3.1–474.3)	3.4 (0.3–29.9)	8.71 ($P < 0.001$)
Left eye only	3	2	7	7	48	45	0.68 (0.16–0.93)	0.56 (−0.05–0.90)	12.0 (1.3–124.2)	7.5 (0.6–91.0)	9.67 ($P < 0.01$)

* *Any eye,* subject has one or more cilioretinal arteries (CRAs) in one or both eyes (i.e., is affected by any kind of CRA); *any location,* subject has a CRA at any location (nasal, temporal, or both); *both eyes,* subject has one or more CRAs in each eye; *left eye/right eye,* subject has one or more CRAs in the left eye/right eye (includes subjects with CRAs in the other eye also); *left eye only/right eye only,* discordant pairs—one twin has CRAs in the left eye/right eye and the other twin does not have CRAs, concordant pairs—both twins have CRAs in the left eye/right eye, and neither has CRAs in the other eye.

† Calculated as the cross product of concordant pairs * nonaffected pairs divided by the cross product of discordant pairs (twin A is proband) * discordant pairs (twin B is proband).

‡ Test of the difference between odds ratios for MZ and DZ twin pairs, taking into consideration the number of pairs in each group. Significant results indicate greater similarity among MZ twins than DZ twins and therefore bolster evidence for genetic influence on the phenotype.

TABLE 4. Result of Structural Equation Modeling for Phenotype Both Eyes, Any Location

Model*	AIC	χ^2	*df*	*P*-Value	*A**†	*D**†	*C**†	*E**†
ACE	−5.7	0.29	3	0.96	0.61 (0.00–0.94)	0.12 (0.00–0.82)	0	0.26 (0.06–0.70)
ADE	−5.7	0.33	3	0.96	0.74 (0.00–0.94)	0	0	0.26 (0.06–0.66)
AE	**−7.7**	**0.33**	**4**	**0.99**	**0.74 (0.34–0.94)**	**0**	**0**	**0.26 (0.06–0.66)**
CE	−6.8	1.24	4	0.88	0	0	0.61 (0.24–0.84)	0.38 (0.16–0.75)
E	1.08	11.1	5	0.05	0	0	0	1 (1.00–1.00)

Boldface type indicates best fitting model.

* Model components: *A,* additive genetic factors; *D,* nonadditive genetic factors; *C,* shared environment, *E,* nonshared environment.

† Proportion of the total variation in prevalence of cilioretinal artery attributable to the model component [% (95% CI)].

was due to additive genetic factors. In *right eye only,* the heritability was 84%, and in *left eye* it was 55%. This means that factors identified as influencing the presence or absence of cilioretinal arteries include additive genetic factors (heritability) and nonshared or random environmental factors unique to the individual. By convention, the latter includes random variation. We found sex to be insignificant when included in the heritability analysis.

DISCUSSION

The present study demonstrated that within a population of 224 twins, the presence or absence of one or more cilioretinal arteries was mainly influenced by genetic factors in all phenotypes. The average heritability of all phenotypes was 71.4%. The relative influence of specific genes versus environmental or random processes was not assessed, because this requires candidate genetic or environmental factors. For cilioretinal arteries, nongenetic effects may include the effects of nonshared intrauterine environment as well as random mechanisms of morphogenesis and measurement errors. The patterns of distribution of retinal vessels are laid out completely at full-term birth.

Some support for a potential impact of preterm health on retinal vessel layout has been found in the observation that preterm birth with a median birth weight of 1250 g is associated with a greater length index for arterioles and fewer numbers of branching points compared with those of children born full term. These vascular abnormalities persist into adulthood.[17] The development of retinal vessels is driven by relative anoxia of the immature avascular retina. The ontogeny of the intraocular blood supply involves programmed elimination of vessels, most notably the hyaloid artery. During these processes of vessel formation, reorganization, and disappearance, cilioretinal arteries may develop, hypothetically, as an enlargement of the anastomoses of the posterior ciliary arteries with small branches from the hyaloid artery on the disc.[18] This theory was supported by a small study of 15 children with birth weights ≤ 2500 g whose prevalence of cilioretinal arteries, 53.3% ($\chi^2 = 5{,}7$; $0{,}01 < P < 0{,}05$), was greater than that of 370 children with normal birth weights (27.3%).[19] Despite the risk of uneven intrauterine nutrition in MZ twins, because of their shared placenta and the risk of anastomoses and transfusion syndrome, this did not have any detectable influence on the prevalence of cilioretinal arteries in this study, as seen by the equal prevalence of cilioretinal arteries in MZ twins and DZ twins. We did not have information about birth weights in the study population, but twins are normally born three to four weeks before term and are on average 1000 g lighter than singletons. This did not appear to have any detectable influence on the development of cilioretinal arteries in this study, since the prevalence of cilioretinal arteries was found to be comparable to that in a previous study of a population with few or no twins.[4] This could be because the twins were healthy and perhaps had almost normal birth weights.

In a phylogenetic perspective there is a systematic variation between species, meaning that the layout of the retinal vessels must be governed by genetics. We found a consistent trend toward MZ twin pairs having higher probandwise concordance rates, odds ratios, and tetrachoric correlations. Insofar as vascular diseases of the posterior pole of the eye are influenced by the layout of the vascular bed, the implication is that there must be an element of congenital hereditary disposition to such disease. All confidence intervals for tetrachoric correlations were wide, suggesting that a larger study may have detected an even stronger genetic effect in all phenotypes. A twin study of the present size does not have enough power to detect a common environmental variance component (*C*) or a nonadditive genetic variance component (*D*), which is indicated also by the wide 95% CI of *A* and *E*.

In summary, structural equation modeling demonstrated a marked additive genetic effect (heritability of 71.4%) and a random environmental effect (28.6%) on the layout of the arterial blood supply of the retina, as represented by the presence or absence of cilioretinal arteries in a population of healthy twins. Understanding the genetic and environmental influence on the architecture of retinal vessels may facilitate elucidation of the pathogenesis of vascular disease in the human retina.

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