Population-Based Estimate of the Sibling Recurrence Risk Ratio for Rhegmatogenous Retinal Detachment

Danny Mitry,[1,2] *Linda Williams,*[1] *David G. Charteris,*[2] *Brian W. Fleck,*[1] *Alan F. Wright,*[3] *and Harry Campbell*[1]

Purpose. The influence of genetic predisposition on nonsyndromic primary rhegmatogenous retinal detachment (RRD) is poorly characterized. The purpose of this study was to investigate the magnitude of genetic risk for RRD.

Methods. All participants (probands) in the Scottish Retinal Detachment Study (N = 922) with known postal addresses were contacted by questionnaire to assess the personal and family history of RRD. Sibling affection status was modeled by logistic regression and generalizing estimating equations accounting for the effect of proband covariates of age, sex, spherical equivalent refraction, index birth order, and body mass index (BMI). Sibling–sibling recurrence risk ratios (λs) and parent–offspring recurrence risk ratios were calculated.

Results. Sixty-five percent of probands returned completed questionnaires. Of these, 602 families (parents, siblings, offspring), 7.8% (47) had one affected member, and 0.5% (3) had two affected members. A total of 501 sibships were included in the regression analysis. The odds ratio (OR) that a sibling would be affected, given another affected sibling, was 1.91 (95% confidence interval [CI], 1.18–3.05). With adjustment for age and sex, the OR that a sibling would be affected increased by 9.8% for each additional diopter of spherical equivalent refractive error (SER) toward myopia in the proband. The λs and the parent-offspring recurrence risk ratio of RRD were 2.1 (95% CI, 1.3–3.2) and 2.9 (95% CI, 1.9–4.2), respectively.

Conclusions. Genetic factors are important in the etiology of myopic and nonmyopic RRD. The risk of having an affected sibling with RRD increases twofold, given that a sibling has had the condition. The sibling risk increases with the level of spherical equivalent myopia in the proband. (*Invest Ophthalmol Vis Sci.* 2011;52:2551–2555) DOI:10.1167/iovs.10-6375

Rhegmatogenous retinal detachment (RRD) is a common ophthalmic emergency that often requires surgical intervention to prevent progression of visual loss. Epidemiologic studies have reported a range of incidence estimates, most commonly, RRD affects between 1 and 2 people per 10,000 annually.[1–3] Several risk factors influence the incidence of RRD: myopia is a major predisposing factor, conferring a 10-fold higher risk of RRD in an eye with a spherical equivalent refractive error > -3 D compared with a nonmyopic eye.[4] Many epidemiologic and genetic studies have demonstrated important genetic influences on the development of myopia.[5] To date, there are more than 15 reported chromosomal regions showing linkage with myopia, the reported range of estimated heritability is between 62% and 90%,[6–8] and the sibling recurrence risk ratio (λs) for myopia (> -2 D) has recently been reported as 2.98 (95% confidence interval [CI], 1.56–5.79).[9] Nonetheless, there have been few studies into the heritability of RRD. Population studies indicate that between 1% and 8.2% of incident cases of RRD also have an affected first-degree relative and recently, the cumulative lifetime risk of RRD has been shown to be 2.6-fold higher in relatives of cases than in those of controls.[10–12] The sibling recurrence risk and its relation to population prevalence (λs) is commonly used in genetic epidemiology to determine the power to detect genetic influences. In this study, we used data from the Scottish Retinal Detachment Study, a 2-year national prospective observational study to calculate the (λs) for RRD. We then examined the effect of sex, proband age at diagnosis, refractive error, birth order, height, and weight on sibling risk.

Methods

The Scottish Retinal Detachment Study was a national, multicenter, observational study that recruited all incident cases of primary retinal detachment in Scotland between November 1, 2007, and October 31, 2009. The methodology and inclusion criteria are described in detail elsewhere.[13] In brief, a case of RRD was defined as an area of subretinal fluid greater than or equal to 2 disc diameters with a full-thickness retinal break identified before or during surgery. This diagnosis was made by a consultant vitreoretinal surgeon after biomicroscopic examination or, in the presence of a fundus obscuring opacity, after B-scan ultrasonography. Subjects with previous posterior segment intraocular surgery, previous penetrating injury in the presenting eye, or RRD in the presenting eye and all other types of retinal detachment (exudative, tractional, and combined) were excluded. In total, 1202 participants were recruited, representing more than 95% of treated cases in Scotland during this period.[2] Demographic data, including age at diagnosis, sex, height (m), and weight (kg), were collected. The ocular parameters of spherical equivalent refraction (SER) and axial length were recorded. Spherical equivalent refractive error SER is defined as (sphere + ½ cylinder) refraction measured in diopters. SER data were taken from focimeter measurement of prescription glasses or by contacting the prescribing optician or optometrist directly. Measurements were rounded to the nearest 0.25 D. In cases in which previous cataract surgery or intraocular surgery was performed, refractive measurements were obtained before any intraocular surgery. If this was not possible, a missing value was assigned.

From the [1]Department of Public Health Sciences, University of Edinburgh, Edinburgh, Scotland, United Kingdom; [2]Moorfields Eye Hospital, London, United Kingdom; and the [3]MRC (Medical Research Council) Human Genetics Unit, Institute of Genetics and Molecular Medicine, Edinburgh, Scotland, United Kingdom.

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Corresponding author: Danny Mitry, Clinical Research Fellow, Department of Public Health Sciences, University of Edinburgh, Teviot Place, Edinburgh, UK; mitryd@gmail.com.

Table 1. The Association of RRD–Affected Index Case Covariates on the Sibling Risk of RRD in a Population of Scottish Families

Covariate	β Coefficient	SE	Wald Statistic	*P*
Intercept	−6.2328	1.1575	29	<0.001
SER	−0.0931	0.0437	4.55	0.028
Age	0.0285	0.0161	3.13	0.077
Female	0.4667	0.4835	0.93	0.334

AIC, 85.53.

Full postal addresses were available for 922 cases. All were white Caucasian and resident in Scotland. After informed consent, each person was contacted by post with a questionnaire. The questionnaire requested information on a diagnosis of retinal detachment in a relative, the height and weight of the proband, birth order of the index case and the affected relative(s), and the size of the family. A cover letter was included encouraging return of the questionnaire even if the family history was negative. The study adhered to the tenets of the Declaration of Helsinki and was approved by the Multi-Centre Research and Ethics Committee Scotland (MREC-06/MRE00/19).

Statistical Methods

A widely used measure of familial aggregation is the λs (sibling recurrence-risk ratio), which is defined as the ratio of risk of disease manifestation, given that one's sibling is affected, compared with the disease prevalence in the general population. The λs expresses the increased risk that an individual has a sibling with RRD will develop the disease and is a quantifiable measure of the genetic contribution to the disease.[14,15] Similarly, the parent–offspring recurrence risk ratio is defined as the proportion of affected parent–offspring pairs among all parent–offspring pairs in a population compared with the normal population prevalence and describes the increased risk of developing the disease in an offspring who has a parent with the disease. The normal population prevalence of RRD in Scotland is unfortunately not known and recent high-quality data on the prevalence of RRD are lacking. However, estimates from the United States indicate a normal prevalence in white Caucasians of 0.7%.[16] We define the prevalence of RRD as the proportion of individuals in the Scottish population that have had an RRD. Based on the age-standardized incidence of RRD in Scotland[2] of 13.09 per 100,000 in men and 7.41 per 100,000 in women and an average life expectancy of 73 years for men and 78 years for women,[17] we estimated the population prevalence of RRD to be 0.96% (13.09× 73/1000) for men and 0.58% for women. The average of these values is 0.77%; thus, we estimate that the normal prevalence of RRD in Scotland is expected to be approximately 0.8%.

To calculate the λs parameter, we used a population approach[18] and the standard formula:

$$\lambda s = Ks/K$$

where *K*s is the sibling recurrence risk, denoted as the proportion of affected siblings among all siblings of affected persons in a population, and *K* is the normal population prevalence of the condition.

Using generalized estimating equations (GEEs) in a logistic regression model with sibling affected status as the binary outcome, we estimated the odds ratio (OR) that a sibling would be affected with RRD, given an affected proband, and examined the effect of proband characteristics on sibling risk. A repeated-measures logistic regression model using GEEs allows the incorporation of covariates and can accommodate different family sizes.[19] In our model, we used a repeated-measures analysis to cluster data by individual family size, such that responses from different families were assumed to be independent and responses within families were assumed to be correlated. Regression covariates examined included proband age at diagnosis, sex, SER, lens status, birth order, and height. Axial length (AL) measurements were available in 40% of the participants but were excluded from the regression analysis due to a high rate of missing data and fewer data points for regression analysis; however, increasing AL correlated strongly with a more myopic SER (r^2 = 0.78).

We used stepwise logistic regression to identify the best-fitting model with the lowest Akaike information criterion (AIC). The AIC is a goodness-of-fit measure of statistical models based on a likelihood function and is commonly used to select between competing statistical models.[20] The main covariates included in the final model were proband age at diagnosis, proband sex, and SER. Proband birth order, height, body mass index (BMI), and lens status were not significantly associated in our regression models and were excluded from the final analysis. There were no significant age–sex interaction terms. Table 1 highlights the model coefficients and associated standard errors. The statistical analyses were performed with R, version 2.1.10, and the software package GEEPACK, version 1.0.17.

Results

In total, we received 602 (65.3%) returned questionnaires from index cases that were included in the analysis. The demographic characteristics between respondents and nonrespondents were similar: age (respondents, mean [SD] age = 60.4 [13] years; nonrespondents, mean [SD] age = 58.9 [16,7] years), sex (respondents, 57% male; nonrespondents, 60.3% male), and SER (respondents mean [SD] SER = −2.56 [3.73] D; nonrespondents mean [SD] = −2.49 [3.72] D). SER was known for 90% of index cases: 51.8% were myopic (> −1), 28.1% were emmetropic, and 9.6% were hypermetropic (> +1). Of all index cases, 78.2% were phakic, 20.1% were pseudophakic, and 1.6% were aphakic at presentation.

Of the 602 families (parents, siblings, and offspring), 7.8% (47) had one affected member, and 0.5% (3) had two affected members. Including all relatives (grandparents to cousins), 12.1% (73) of probands had a relative affected with RRD, and eight families had two or more affected individuals. In total, 83.2% (501/602) of probands had one or more siblings. Sibship size ranged from 2 to 12 in 501 families, with a mean of 2.5 siblings per family. Tables 2 and 3 highlight the distribution of

Table 2. Highlights the Relative Distribution of the Family Members of Each Index Case Affected with RRD

Family Members	Number Affected with RRD	Total Number of Family Members*
Parent		
Father	13	602
Mother	15	602
Paternal		
Grandfather	0	
Aunt	3	850
Uncle	3	808
Cousin	1	2633
Maternal		
Grandfather	4	
Aunt	3	777
Uncle	4	704
Cousin	5	2623
Siblings		
Brother	12	666
Half–brother	0	
Sister	8	590
Half–sister	1	
Offspring		
Son	1	535
Daughter	3	515

* Includes deceased members and half siblings.

Table 3. Number of Families by Size and Number of Cases of RRD among 3,510 Relatives of 602 Probands

	Number of Individuals with RRD†				
Family Size*	**0**	**1**	**2**	**3**	**Total**
2	22	3		–	25
3	46	5		–	51
4	86	6	1	–	93
5	106	10		–	116
6	92	9	1	–	102
7	60	6		–	66
8	41	0	1	–	42
9	31	1		–	32
10	15	1		–	16
11	13	0		–	13
12	11	3		–	14
13	6	0		–	6
14	0	2		–	2
15	2	0		–	2
NA	21	1		–	22
Total	552	47	3	–	602

NA, not available.
* Includes parents, siblings and offspring.
† Index cases are excluded.

affected family members and the frequency of affected members by family size.

Logistic regression model coefficients are shown in Table 1 and are based on all families with at least two siblings (n = 501). The OR of a sibling's risk of RRD, given an affected sibling, is 1.91 (95% CI, 1.18–3.05). Of the covariates examined, the degree of myopia of the proband demonstrated a significant effect on sibling risk. An increase of 1 D of myopia in the proband resulted in a 9.8% increased risk to a sibling for RRD. Table 4 highlights the increasing odds of RRD in a sibling by the increasing level of myopia in the proband.

Assuming a population prevalence of 0.8%, the λs for RRD is 2.1 (95% CI, 1.3–3.2) [(21/1256)/(0.8/100)], and the parent–offspring recurrence risk ratio is 2.9 (95% CI – 1.9–4.2) [(28/1204)/(0.8/100)]. Table 5 highlights the λs for the different classifications of RRD.

Discussion

Our data provide evidence that genetics and heritability play an important role in the predisposition to RRD. The familial data used in the study were ascertained through the Scottish Retinal Detachment Study, which was a large prospective observational study with a clear case definition and a high (>90%) ascertainment rate of incident cases that derived from the entire resident population of Scotland. In the present study of 501 Scottish sibships, the risk of having an affected sibling with RRD is increased nearly twofold, given that one sibling has had the condition. We examined the effect of proband age, sex, height, weight, birth order, lens status, and spherical equivalent refraction on the sibling risk. Of these, an increase in spherical equivalent refractive error of 1 D toward myopia in the proband conferred a significant increased risk of RRD to a sibling of 9.8% adjusting for the proband's age and sex.

Table 4. OR of a Sibling Developing RRD as a Function of the Level of Myopic Equivalent Refraction in the Affected Index Case

SER of Proband (D)	OR and CI That a Sibling Is Affected with RRD
−1	1.1 (1.01–1.20)
−2	1.23 (1.1–1.32)
−3	1.37 (1.21–1.45)
−4	1.52 (1.33–1.59)
−5	1.69 (1.46–1.75)
−6	1.87 (1.62–2.00)

With adjustment for age and sex, each additional diopter of myopia in the index case increases the odds of RRD in a sibling by 9.8%.

Table 5. The Sibling Recurrence Risk Ratio by Sex, Myopia, and Lens Status of Index Cases with RRD Derived from a Scottish Population of 501 Sibships

	Sibling Recurrence Risk Ratio λs (95% CI)
All RRD cases	2.1 (1.3–3.2)
Male index	1.8 (1.0–3.5)
Female index	2.9 (1.4–5.1)
Index age ≤60 y	2.3 (1.0–4.3)
Index age >60 y	2.4 (1.1–4.1)
Nonmyopic RRD	1.9 (1.1–3.2)
Myopic RRD (>−1 D)	2.8 (1.5–4.6)
Phakic RRD only	2.5 (1.5–3.9)
Pseudophakic or aphakic RRD only	2.0 (0.4–5.9)

The present study, however, should be understood in the context of its limitations. An incomplete questionnaire response rate (65%) may lead to participation bias if persons with an affected sibling are more or less likely to participate. However, all participants were encouraged to return the questionnaire regardless of family history, and comparison of the demographic characteristics between responders and nonresponders did not show significant differences. The diagnosis of RRD in family members was ascertained through a self-reported questionnaire, which may similarly have introduced bias; however, RRD is most commonly an acute condition causing visual loss requiring surgical intervention, and thus its nature is likely to be remembered with a degree of accuracy. Also, the conclusions on the genetic influences of RRD reached by this study depend on inherent assumptions in the design and statistical models used. Our demonstration of the familial aggregation of RRD has been derived through contacting all incident cases; thus, we cannot comment on the risk of RRD in relatives of unaffected controls. We have sought to model the OR of RRD in a sibling accounting for relevant changes in proband characteristics known from previous epidemiologic studies to affect RRD incidence. There may be other shared environmental factors that contribute to the familial aggregation observed and finally, the model we have used has no way of accounting for potential gene–environment interactions.

In this study, we estimate the λs and the parent offspring recurrence risk ratio of RRD to be 2.1 (95% CI, 1.3–3.2) and 2.9 (95% CI, 1.9–4.2), respectively. Hence, the estimated prevalence of RRD in siblings of affected cases is twice that of the normal population prevalence (1.68% vs. 0.8%). The λs parameter is directly related to the power of genetic studies; however, its estimate is subject to bias and is dependent on the prevalence of affection in the overall population. The λs diminishes linearly as the overall population prevalence approaches unity,[18,21] and over- or underestimation of population prevalence can thus dramatically affect the estimated λs. To our knowledge, there have been no previous estimates of the λs of RRD; however, our finding is similar to previous reports of moderate myopia > −2 D (2.52 – 95% CI, 1.51–5.87)[9] but less than the reported values for high myopia (reported range, 4.9−20).[18,22] The λs for phakic RRD is higher than for pseudophakic or aphakic RRD (Table 5), suggesting

that nongenetic factors may have a greater influence on RRD after cataract surgery. The sibling recurrence risk for complex ocular traits with a proven genetic component such as age-related macular degeneration has been demonstrated to be modest (λs or $Ks = 2.96$).[23] In general, however, the higher the λs value (>5), the more likely a significant genetic contribution to the pathogenesis of disease exists, although the relationship between an underlying disease-susceptibility allele and λs is complex.[24,25]

Familial aggregation studies of RRD are uncommon because of the low frequency of the condition; however, Go et al.[11] have demonstrated a threefold increased frequency of RRD in siblings of affected subjects compared with siblings of unaffected subjects. Accounting for myopia, age, and sex did not fully explain the familial aggregation observed. We similarly noted that the odds that a person would have RRD is significantly increased (OR, 1.91: 95% CI, 1.18–3.05) if sibling had the condition. Go et al.[11] report a higher frequency of RRD in relatives of myopic probands and controls compared to nonmyopic probands and controls (1.13% vs. 0.33%), and it is interesting that they found a higher frequency of RRD in relatives of myopic probands than in myopic controls (1.8% vs. 0.6%), suggesting that genetic factors other than those controlling myopia influence RRD pathogenesis, but that myopia genes may influence other putative genetic determinants of RRD. Our regression analysis similarly demonstrates that an increasing degree of myopia in the proband increases the sibling risk of RRD (by approximately 10% for each spherical equivalent diopter), but this does not completely account for the familial aggregation observed. The λs for nonmyopic RRD is 1.9 (95% CI, 1.1–3.2), which, although lower than the estimate for myopic RRD (2.8 [95% CI, 1.5–4.6]) nonetheless highlights the presence of a genetic component to RRD not associated with myopia.

Myopia and in particular high myopia are one of the most relevant risk factors for RRD development. Several studies have highlighted the importance and the complexity of genetic influences on the etiology of these traits and to date numerous chromosomal regions have been identified through genetic linkage[26–28] and more recently genome-wide association studies.[29] Marked variability in heritability has been demonstrated between different ethnic populations and the relevance of environmental influences has been confirmed.[9,30–31] In a similar way, the genetic influence of RRD is likely to be complex and multifactorial and may demonstrate similar ethnic variation, as has been noted in population-based incidence studies.[32,33]

Genetic studies of RRD not associated with known syndromes (such as Stickler's syndrome or Wagner's syndrome) are in their infancy, and there are few reports confirming linkage to chromosomal regions for nonsyndromic RRD.[34] Known regions involved in collagen development have been implicated in causing RRD in association with other vitreous abnormalities and may provide potential candidate genes.[35] Similarly, genes coding for components involved in vitreoretinal adhesion, such as laminin and fibronectin may prove to play a part in the pathogenesis of this condition. Despite its limitations, our study, in which the sample was derived from a large, well-characterized, stable Caucasian population, highlights that familial occurrence of RRD is a risk factor for its development, proband refractive error significantly influences sibling risk independent of age at diagnosis and sex and that genetic factors are likely to be important in the etiology of nonmyopic RRD.

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