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Using the Utah Population Database to assess familial risk of primary open angle glaucoma

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ABSTRACT

Purpose: Primary open angle glaucoma (POAG) is a leading cause of irreversible blindness in the elderly. Previous epidemiological studies have identified family history, ethnic origin, age, high intraocular pressure and diabetes mellitus as risk factors. However, it is difficult to assess the extent family history plays in this disease process. The Utah Population Database (UPDB), created by the University of Utah, has recently become a resource for which greater than 9 million records are available for use. The UPDB is divided into two major data sets from which family members can be identified, namely 1.6 million genealogy records and 2 million Utah birth certificates. This study utilizes these resources to assess the familial risk of POAG within the Utah Population.

Methods: The University of Utah's hospital and clinic records were searched for patients with primary and chronic open angle glaucoma (ICD9 codes 365.04 and 365.11) between the years 1995 and 2005. A case-control analysis was then performed with specialized UPDB software that was modified to constrain the control and pedigree populations to over 1 million University of Utah-UPDB linked records. Controls were matched to cases by gender and birth year (±2.5 years) with only one control being used per case. Population-attributable risk (PAR) to familial factors and relative risk (RR) were computed using conditional logistic regression (CLR).

Results: From the original 1.5 million medical records, 6198 patients with glaucoma were identified. Of these, 3391 met the inclusion criteria, which required patients to have at least one parent or one child in the UPDB. The PAR in this population was found to be 0.20, indicating 20% of the risk for glaucoma is attributable to genetic factors. CLR computations also showed a significantly increased relative risk ($p < 0.05$) in first cousins (RR = 1.45 (95% confidence interval (CI) 1.16–1.8)), second cousins (RR = 1.19 (95% CI 1.08–1.32)), siblings (RR = 3.76 (95% CI 2.66–5.31)), parents (RR = 6.25 (95% CI 3.94–9.9)) and children (RR = 6.77 (95% CI 3.39–13.5)).

Conclusions: Based on these familial data, there is a significantly higher prevalence of glaucoma in both first and second generation relatives of those affected as compared to relatives in the control group. When compared with other epidemiologic studies, such as an analysis of first-degree relatives of patients from the Rotterdam study, which showed a PAR of 16%, our study actually demonstrates a greater familial contribution to glaucoma. The UPDB is a valuable and unique resource providing a large population from which to analyze the familial risk of glaucoma.

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1. Introduction

Primary open angle glaucoma (POAG) is the world's second most common cause of irreversible blindness in the elderly (Quigley, 1996). Several large population-based studies have found the prevalence of POAG to range from 1.1% to 3.0% in predominately white populations (Coffey et al., 1993; Dielemans et al., 1994; Klein et al., 1992; Mitchell, Smith, Attebo, & Healey, 1996; Tielsch et al., 1991) and 4.2% to 8.8% in black populations (Leske, Connell, Schachat, & Hyman, 1994; Mason et al., 1989; Tielsch et al., 1991). Additionally, it is predicted that the anticipated increase in the population over 40 years of age between 2010 and 2020 will cause a 30% rise in the prevalence of glaucoma during this time period, from 60.5 million to 79.6 million people (Quigley & Broman, 2006).

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Open angle glaucoma is distinguished by loss of peripheral visual function resulting from retinal ganglion cell death and progressive atrophy of the optic nerve. It is characterized by an excavated appearance of the optic disc on exam (Quigley, 1993). The disease is often associated with elevated intraocular pressure (IOP) (Leske, 1983) and decreased retinal nerve fiber layer thickness and optic disc rim area, both of which indicate loss of retinal ganglion cells (Jonas, Budde, & Panda-Jonas, 1999; Quigley, 1999; Tuulonen & Airaksinen, 1991).

While the cause of POAG is unclear, previous epidemiological studies have identified family history, ethnic origin, age, and elevated IOP as risk factors (Tielsch, Katz, Sommer, Quigley, & Javitt, 1994; Wolfs et al., 1998). Other reported risk factors include diabetes mellitus, hypertension, and lifestyle factors such as smoking and alcohol consumption (Daubs & Crick, 1981; Dielemans et al., 1995; Katz & Sommer, 1988; Klein, Klein, & Jensen, 1994; Mitchell, Smith, Chey, & Healey, 1997; Tielsch, Katz, Quigley, Javitt, & Sommer, 1995; Wilson, Hertzmark, Walker, Childs-Shaw, & Epstein, 1987). However, many of these reported associations are still under debate (Klein, Klein, & Ritter, 1993; Leske, Wu, Hennis, Honkanen, & Nemesure, 2008; Tielsch et al., 1995; Tielsch, Katz, Sommer, Quigley, & Javitt, 1995).

Many clinical studies have documented the familial aggregation of POAG. First-degree relatives of patients with POAG have a reported 7–10-fold increased risk of developing the disease when compared to the general population (Drance, Schulzer, Thomas, & Douglas, 1981; Wolfs et al., 1998). Additionally, Teikari et al. observed a high concordance of disease between monozygotic twins (Teikari, 1987). Other studies have performed genome-wide scans that have revealed 20 possible genetic loci (Supplementary Table 1). One promising locus is GLC1I. Allingham et al. showed that it contributed an estimated 17% attributable risk in 15 out of 86 multiplex families with POAG stratified for analysis on the basis of age of onset of disease (Allingham et al., 2005). Woodroffe et al. corroborated that one or more genes on this locus may account for over half of the POAG families in their cohort (Woodroffe et al., 2006). The number of loci associated with POAG, therefore, provides strong evidence for the polygenic nature of this disease. Recent work has identified three additional genes (MYOC, OPTN, WDR36) associated with POAG (Monemi et al., 2005; Rezaie et al., 2002; Stone et al., 1997). Although these discoveries are promising, it is estimated that these three genes likely contribute to the pathogenesis of POAG in <5% of cases in the general population (Alward et al., 2002, 2003; Fingert et al., 1999; Hewitt, Dimasi, Mackey, & Craig, 2006; Leung et al., 2003). Thus, it seems that the genetic explanation for a significant percentage of POAG patients is yet to be discovered.

While it seems clear that family history contributes to glaucoma susceptibility, the degree to which genetics plays a role is not apparent. Large pedigrees of glaucoma patients may aid current and future genetic association studies by demonstrating the heritability of glaucoma-contributing genes, or even uncovering related genetic polymorphisms. The Utah Population Database (UPDB), created by the University of Utah, is a resource of over 9 million records, which can be utilized to identify large pedigrees of families affected by different diseases. Other studies have used the database to investigate the familial aggregation of ocular disease, such as AMD (Luo et al., 2008). The appeal to perform genetic research in Utah has been described by us previously and stems from Utah's unique population of larger families and minimization of environmental factors (Luo et al., 2008). The purpose of this study was to utilize UPDB to assess the familial risk of POAG.

2. Methods

The study is a population-based retrospective case-control study utilizing data from the UPDB. The UPDB contains data from the Family History Library maintained by the Church of Jesus Christ of Latter-Day Saints (LDS), Utah State Department of Health, and other statewide data sets (http://www.hci.utah.edu/groups/ppr/data.html). The UPDB is linked to the University of Utah Health Sciences Center (UUHSC) and allows for the identification of large pedigrees. From this, calculations of population-based risks of disease, such as POAG, can be determined. Previous work in our lab has described this data set and how it can be used in identifying affected families (Luo et al., 2008).

This study has been approved by the University of Utah IRB and the Utah Research for Genetic and Epidemiological Research (RGE). The RGE is the administrative body for the UPDB (Wylie & Mineau, 2003).

2.1. Open angle glaucoma cases

The University of Utah's 1.5 million hospital and clinic records were searched for patients with primary and chronic open angle glaucoma (ICD9 codes 365.04 and 365.11) between the years 1995 and 2005. A total of 6198 patients were identified. Inclusion criteria required patients to have at least one parent or one child in the UPDB in order to be used for further familial statistical assessments. Of the cases identified, 3391 had adequate pedigree information in the UPDB and were included in the population-attributable risk (PAR) and relative risk (RR) analyses.

2.2. Population controls

After identification of POAG cases, controls were chosen from the UUHSC-UPDB cohort. Only controls with family information recorded in the UPDB were used for the study. Controls were matched to cases by gender, birth year (±2.5 years), presence in the linked UUHSC-UPDB set, and absence of POAG diagnosis. One control was selected for each case and each control was unique. The controls were chosen from UUHSC database where a normal eye examination was recorded.

A case-control analysis was then performed with specialized UPDB software that was modified to constrain the control and pedigree populations to over 1 million UUHSC-UPDB linked records. PAR and RR were computed using conditional logistic regression (CLR).

2.3. Statistical analyses

2.3.1. Familial standardized incidence ratio (FSIR)

The FSIR (Kerber, 1995) permits quantification of an individual's familial risk of disease, taking into account the number of biological relatives, degree of relatedness to the proband, and person-time at risk among family members. FSIR is calculated by tabulating the observed and expected numbers of cases of disease among all of an individual's relatives, weighting the contribution of each relative by the probability that the relative shares an allele with the subject by common descent. Boucher and Kerber describe an empirical Bayes adjustment for measurement error (Boucher & Kerber, 2001).

2.3.2. Population-attributable risk

PAR was calculated using a conditional logistic regression method described by Bruzzi (Bruzzi, Green, Byar, Brinton, & Schairer, 1985). First, a conditional logistic regression model is used to predict relative risk as a function of FSIR. From this model, individual probabilities of causation for each case are computed as (RR-1)/RR, where RR is the relative risk estimated from the model for the observed level of FSIR. The mean probability of causation across all the cases is the population-attributable risk.

2.3.3. Relative risks

RRs for parents, siblings, and first and second cousins of the 3391 cases were calculated using unconditional logistic regression, following the method described by Bai et al. (Bai, Sherman, Khoury, & Flanders, 2000).

2.3.4. Pedigree p-values

The probability of a family having some observed number of cases (x), under the null hypothesis of no familial disease aggregation, is the Poisson probability of $X \geqslant x$ given an expected number, μ.

3. Results

From the original 1.5 million medical records, 6198 patients with glaucoma were identified. Of these, 3391 patients met inclusion criteria and were used in the study. The POAG cases and controls were analyzed to determine various risks of disease development by relation to the proband in order to demonstrate the familial risk of POAG. Cases and controls are displayed in Table 1.

The PAR was found to be 0.14 and the adjusted PAR was found to be 0.20, indicating 20% of the risk for glaucoma is attributable to a genetic factor (Table 2). CLR computations also showed increased RR in first cousins, second cousins, siblings, parents, and children of the proband (Table 1).

Eleven large pedigrees having at least 5 affected family members are shown in Table 3. These families have a significantly increased FSIR (p-value < 0.05), indicating a greater prevalence of glaucoma when compared to the population controls, and, further underscoring the familial aggregation of POAG in the Utah Population. The kinship analysis software provided each family with a founder Person ID, number of descendents, observed number of affected, expected number of affected, FSIR, and standard error. Data such as birth year, death year, and gender on pedigree founders and all affected cases was given for each familial cluster. Findings were reviewed and careful manual analysis of each affected case identified in the clusters was performed. Large pedigrees were drawn out using Peddraw software, two of which are shown in Figs. 1a and 1b. Twenty-two families were identified as having five or more living affected family members. In each family, the p-value under the null hypothesis of no familial disease aggregation is <0.05 and the FSIR is >.0. The family members within the pedigrees were compared and reduced to 11 extended large families due to common ancestry. In some instances multiple founders were identified for the same group of cases, which is annotated in Table 3 with the cluster number followed by a letter corresponding to the different founder. Of the 3391 individuals with POAG from the study cohort, 138 individuals fall into the 11 extended pedigrees. Descendents and FSIR for each family ranged from 547 to 6968 and 2.91 to 14.37, respectively (Table 3). Likewise, the median number of descendents and median FSIR in each pedigree was 2298 and 5.15 respectively, derived from the data in Table 3. The large number of descendents and elevated FSIR indicate a strong familial aggregation of POAG in Utah families.

Table 2
Population-attributable risk (PAR) for POAG.

Attributable Risk (CLR)		
	PAR	CI
Raw	0.14	0.10–0.17
Adjusted	0.20	0.13–0.26

Table 3
Eleven families identified from the Utah Population Database.

Cluster	Descendants	Observed	Expected	FSIR	p-Value
Cluster 1a	6110	13	4.4651	2.9115	0.0008
Cluster 1b	3334	8	2.0278	3.9452	0.0012
Cluster 1a	1480	6	0.8622	6.9592	0.0003
Cluster 1c	1814	5	1.2846	3.8922	0.0102
Cluster 1d	6968	12	4.8393	2.4797	0.0043
Cluster 2a	547	5	0.3481	14.3651	0
Cluster 2b	1633	5	1.2289	4.0687	0.0085
Cluster 2c	1129	5	0.7733	6.4661	0.0012
Cluster 2d	1198	5	0.9173	5.4507	0.0025
Cluster 3	1581	5	1.1006	4.5429	0.0054
Cluster 4	2192	5	1.3715	3.6457	0.0132
Cluster 5a	1107	5	0.5206	9.6034	0.0002
Cluster 5b	1328	5	0.7309	6.8409	0.001
Cluster 6	1229	5	1.0571	4.7301	0.0046
Cluster 7	3126	9	2.5837	3.4834	0.0014
Cluster 8	2492	6	1.9213	3.1228	0.0139
Cluster 9	2158	5	1.1768	4.2487	0.0072
Cluster 10	2342	7	1.906	3.6726	0.0035
Cluster 11a	2627	6	1.4913	4.0234	0.0043
Cluster 11b	1980	5	1.0528	4.7494	0.0045
Cluster 11c	2091	6	1.2151	4.9377	0.0016
Cluster 11d	2099	5	0.9735	5.1363	0.0033

4. Discussion

Our study confirms a genetic component to POAG, which is likely to have a complex, multifactorial inheritance pattern. Based on the familial data gathered from the UUHSC-UPDB cohort, there is a significantly higher prevalence of glaucoma in both first and second degree relatives than the relatives in the control group (p-value < 0.05). While previous studies have shown that first-degree relatives of glaucoma patients have the highest risk of developing glaucoma, some of these studies do not consider second degree relatives (Leighton, 1976; Sung et al., 2006). Data on relatives extending beyond first degree is less studied, and an increased relative risk in both first (RR = 1.45) and second (RR = 1.19) cousins as shown by this study may indicate a stronger genetic component to POAG than previously recognized, especially when taking into account the small number of alleles shared by second cousins (2%). Furthermore, a design looking at only first-degree relatives may underestimate the genetic nature of glaucoma, especially if incomplete penetrance of glaucoma genes is present (Green et al., 2007).

Our study found the PAR of POAG to be 20%. Other epidemiologic analysis, such as the study by Wolfs, which analyzed first-degree relatives of patients from the Rotterdam study, showed a

Table 1
Number of cases, controls and relative risk of different relationships to probands for POAG.

Relationship	Cases (n = 3391)		Controls (n = 3391)		Relative risk (95%CI)	p-Value
	Affected	Unaffected	Affected	Unaffected		
Parent	141(3.28%)	4159(96.72%)	20(0.54%)	3677(99.46%)	6.25(3.94–9.9)	5.7×10^{-15}
Sibling	154(7.35%)	1942(92.65%)	42(2.11%)	1949(97.89%)	3.76(2.66–5.31)	6.12×10^{-14}
First cousin	195(2.14%)	8922(97.86%)	138(1.48%)	9215(98.52%)	1.45(1.16–1.8)	0.00104
Second cousin	813(1.61%)	49709(98.39%)	728(1.36%)	52895(98.64%)	1.19(1.08–1.32)	0.000601

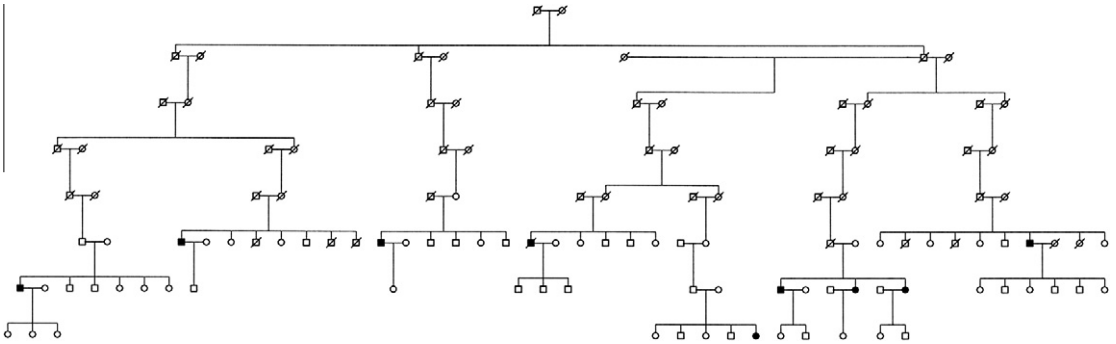

Fig. 1a. POAG Family 1 Pedigree.

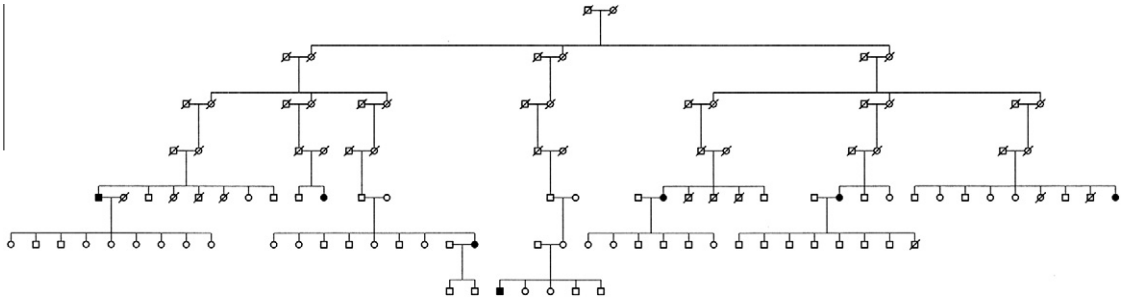

Fig. 1b. POAG Family 2 Pedigree.

PAR of 16% (Wolfs et al., 1998). In comparison, this study shows a greater familial contribution to glaucoma. This may be due to the large number of patients used in our population ($n = 3391$) compared to the Rotterdam study ($n = 48$). As previously described by our lab, the UPDB is a biologically representative sample of a broad spectrum of the United States Caucasian population and has a similar genetic makeup to other Northern European-derived populations (Luo et al., 2008). Additionally, Goldgar et al. reported that the relative risks of cancer and other diseases calculated for the Utah Population are similar to published estimates of other populations (Goldgar, Easton, Cannon-Albright, & Skolnick, 1994). Furthermore, consanguinity rates in Utah are similar to the US population as described by Jorde (1989) and McLellan, Jorde, and Skolnick (1984). Thus, we feel that the relative risk calculations from the UPDB can be applied to other communities.

The extensive POAG pedigrees identified in this study may help shed further light on the genetics and pathogenesis of POAG. We have contacted several members of these large pedigrees and collected blood samples and additional data, which may become more valuable as new genetic discoveries are made. Additionally, while the possibility of underlying genetic heterogeneity for disease may dampen the excitement of linkage studies, this limitation may be attenuated by extended pedigrees with large numbers of affected patients. A few large, independently informative pedigrees, such as those identified in this study, may help find new linked regions for POAG and provide more clarity and narrower regions in currently identified loci. Furthermore, the large number of descendents and elevated FSIR within these large pedigrees indicate a strong familial aggregation of POAG in Utah families, thus showing the utility of the linked UPDB-UUHSC records and kinship analysis software in providing the basis to identify and recruit extended families with clustering of POAG.

Our study is not without limitations. The number of cases in the UUHSC-UPDB cohort may be somewhat conservative from underdiagnosis due to selection bias, as an assumption of unaffected status was made when there was no POAG diagnosis recorded in the UUHSC system. The UUHSC system is only one of many healthcare providers in the state of Utah and some POAG patients are certainly receiving care from other providers. However, the UPDB is currently working with these providers to incorporate their medical records into our database, which would help further delineate POAG status in our study population. Our study is ongoing and we will re-assess our population periodically in the future to include newly collected patient data into our database.

Another limitation of our study is the lack of environmental data such as diet and smoking history. This was not included in the UPDB and was not collected at the time of this study. However, this data can be collected in the future and may prove useful in enhancing further study efforts.

The PAR and RR findings in this study demonstrate the familial aggregation of POAG in the Utah Population. Due to the genetic make up of the cohort and its similarity to other populations in the U.S. and elsewhere, these findings can reasonably be extended to other communities. Our risk assessment and pedigree findings contribute to the understanding of the role of genetics in POAG, and this may lead to a better understanding of the pathogenesis of POAG in the future. The UPDB is a valuable and unique resource providing a large population from which to analyze familial risk and large pedigrees with several affected members of glaucoma, and may be used in future research for genetic analysis of other common ocular diseases such as diabetic retinopathy.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.visres.2010.09.018.

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