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).
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, & Pandas-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 affected families (Luo et al., 2008).

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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 $X \geq x$ given an expected number, $\mu$.

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 > 1.0. 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 6968 and 2.91 to 14.37, respectively (Table 3). Likewise, the median number of descendents and median FSIR in each pedigree was 6968 and 2.91 to 14.37, respectively (Table 3). The large number of descendents and elevated FSIR indicate a strong familial aggregation of POAG in Utah families.

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>
<thead>
<tr>
<th>Relationship</th>
<th>Cases (n = 3391)</th>
<th>Controls (n = 3391)</th>
<th>Relative risk (95%CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent</td>
<td>Affected 141(3.28%)</td>
<td>Unaffected 4159(96.72%)</td>
<td>0.54(0.39-0.79)</td>
<td>3.01 x 10-15</td>
</tr>
<tr>
<td>Sibling</td>
<td>Affected 157(4.75%)</td>
<td>Unaffected 1942(95.25%)</td>
<td>2.09(1.56-2.81)</td>
<td>0.00012</td>
</tr>
<tr>
<td>First cousin</td>
<td>Affected 195(2.14%)</td>
<td>Unaffected 8922(97.86%)</td>
<td>1.38(1.25-1.51)</td>
<td>0.00009</td>
</tr>
<tr>
<td>Second cousin</td>
<td>Affected 813(1.61%)</td>
<td>Unaffected 49709(98.39%)</td>
<td>1.27(1.14-1.41)</td>
<td>0.00012</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>PAR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.14</td>
<td>0.10-0.17</td>
</tr>
<tr>
<td>0.20</td>
<td>0.13-0.26</td>
</tr>
</tbody>
</table>

Table 3
Eleven families identified from the Utah Population Database.
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.

Acknowledgments

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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.