Available online at www.sciencedirect.com
ScienceDirect
Vision Research 48 (2008) 494–500
Vision Research
www.elsevier.com/locate/visres

Familial aggregation of age-related macular degeneration in the Utah population

Ling Luo [a,b,c,1], Jennifer Harmon [a,b,1], Xian Yang [a,b], Haoyu Chen [a,b], Shrena Patel [a,b,e], Geraldine Mineau [d], Zhenglin Yang [a,b,f], Ryan Constantine [a,b], Jeanette Buehler [a,b], Yuuki Kaminoh [a,b], Xiang Ma [a,b], Tien Y. Wong [g], Maonian Zhang [c,*], Kang Zhang [a,b,*]

[a] *Department of Ophthalmology and Visual Sciences, Moran Eye Center, University of Utah School of Medicine, Salt Lake City, UT 84132, USA*
[b] *Program in Human Molecular Biology & Genetics, Eccles Institute of Human Genetics, University of Utah School of Medicine, Salt Lake City, UT 84132, USA*
[c] *Department of Ophthalmology, The Chinese Military Post-Graduate Medical School, The 301 hospital, Beijing 100853, China*
[d] *Department of Oncological Sciences, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT 84112, USA*
[e] *Primary Children's Medical Center Foundation Scholar, Division of Neonatology, Department of Pediatrics, University of Utah School of Medicine, Salt Lake City, UT 84112, USA*
[f] *Sichuan Medical Science Academy & Sichuan Provincial People's Hospital, Sichuan 610071, China*
[g] *Centre for Eye Research Australia, University of Melbourne, Vic., Australia*

Received 5 July 2007; received in revised form 12 November 2007

Abstract

We examined familial aggregation and risk of age-related macular degeneration in the Utah population using a population-based case-control study. Over one million unique patient records were searched within the University of Utah Health Sciences Center and the Utah Population Database (UPDB), identifying 4764 patients with AMD. Specialized kinship analysis software was used to test for familial aggregation of disease, estimate the magnitude of familial risks, and identify families at high risk for disease. The population-attributable risk (PAR) for AMD was calculated to be 0.34. Recurrence risks in relatives indicate increased relative risks in siblings (2.95), first cousins (1.29), second cousins (1.13), and parents (5.66) of affected cases. There were 16 extended large families with AMD identified for potential use in genetic studies. Each family had five or more living affected members. The familial aggregation of AMD shown in this study exemplifies the merit of the UPDB and supports recent research demonstrating significant genetic contribution to disease development and progression.

Keywords: Age-related macular degeneration; Genetic epidemiology; Genetics

1. Introduction

Age-related macular degeneration (AMD) is the most common cause of vision loss in elderly individuals in the developed world (Hageman et al., 2001; Kaplan, Leibole, Tezel, & Ferguson, 1999; Klein, Klein, & Linton, 1992; Krzystolik et al., 2002; Okamoto et al., 1997; Penfold, Killingsworth, & Sarks, 1985; Vingerling et al., 1995). Early AMD is characterized by drusen deposition and hyper- or hypo-pigmentation of the retinal pigment epithelium (RPE) without vision loss (Fig. 1B). Advanced AMD can be classified into two categories: geographic atrophy (GA), characterized by atrophy of the RPE (Fig. 1C), and choroidal neovascularization (CNV, wet AMD, Fig. 1D). Estimates suggest that 1.75 million people in

* Corresponding authors. Fax: +1 801 587 7686 (K. Zhang).
E-mail addresses: zhangmaonian@medmail.com.cn (M. Zhang), kang.zhang@hsc.utah.edu (K. Zhang).
[1] These authors contributed equally to this work.

0042-6989/$ - see front matter © 2008 Published by Elsevier Ltd.
doi:10.1016/j.visres.2007.11.013

the United States suffer from advanced AMD and 8 million people are affected by early AMD, putting them at risk to develop advanced disease (Friedman et al., 2004).

AMD is a multi-factorial disease involving the interplay of genes and environmental factors. Various twin and sib studies have demonstrated a high concordance of AMD development (Meyers, Greene, & Gutman, 1995; Seddon, Cote, Page, Aggen, & Neale, 2005), and previous population studies have also highlighted the heritability of AMD (Heiba, Elston, Klein, & Klein, 1994; Klaver et al., 1998; Klein, Klein, Lee, Moore, & Danforth, 2001; Seddon, Ajani, & Mitchell, 1997). The most convincing evidence for genetic contribution in AMD is the identification of major disease susceptibility alleles on chromosomes 1q32 (CFH region) and 10q26 (LOC387715/HTRA1 region). Specifically, the risk of developing AMD is associated with the C allele of the Y402H variation in CFH (Edwards et al., 2005; Hageman et al., 2005; Haines et al., 2005; Klein et al., 2005; Zareparsi et al., 2005). In addition, a single nucleotide polymorphism, rs11200638, located in the promoter region of the *HTRA1* gene, confers a significant increase in the risk of developing advanced AMD (Cameron et al., 2007; Dewan et al., 2006; Yang et al., 2006). Other research has focused on investigating environmental risk factors that may contribute to AMD, such as smoking, which has an associated odds ratio ranging from 1.8 to 3 (Smith et al., 2001).

However, the exact contribution and relative importance of genetic and environmental factors in AMD pathogenesis remains uncertain (van Leeuwen, Klaver, Vingerling, Hofman, & de Jong, 2003). Few studies have established familial patterns of susceptibility, which may prove important in elucidating the relationship between genetic and environmental components in AMD. Large AMD pedigrees may complement current and future genetic association studies by revealing the heritability of AMD disease-contributing genes. These pedigrees may help demonstrate disease causation related to specific polymorphisms. The Utah Population Database (UPDB) can help identify large pedigrees of AMD families to potentially be utilized in various studies such as linkage analysis and mode of genetic transmission.

The appeal of studying AMD in the Utah population is also magnified when assessing the state's demographic data. During the second half of the 19th century, the average number of children per couple was 7.7 for once-married women (Bean, Mineau, & Anderton, 1990). Utah residents continue to have large families, reporting an average family size of 3.57, as compared to 3.14 for the U.S. overall (www.gover-

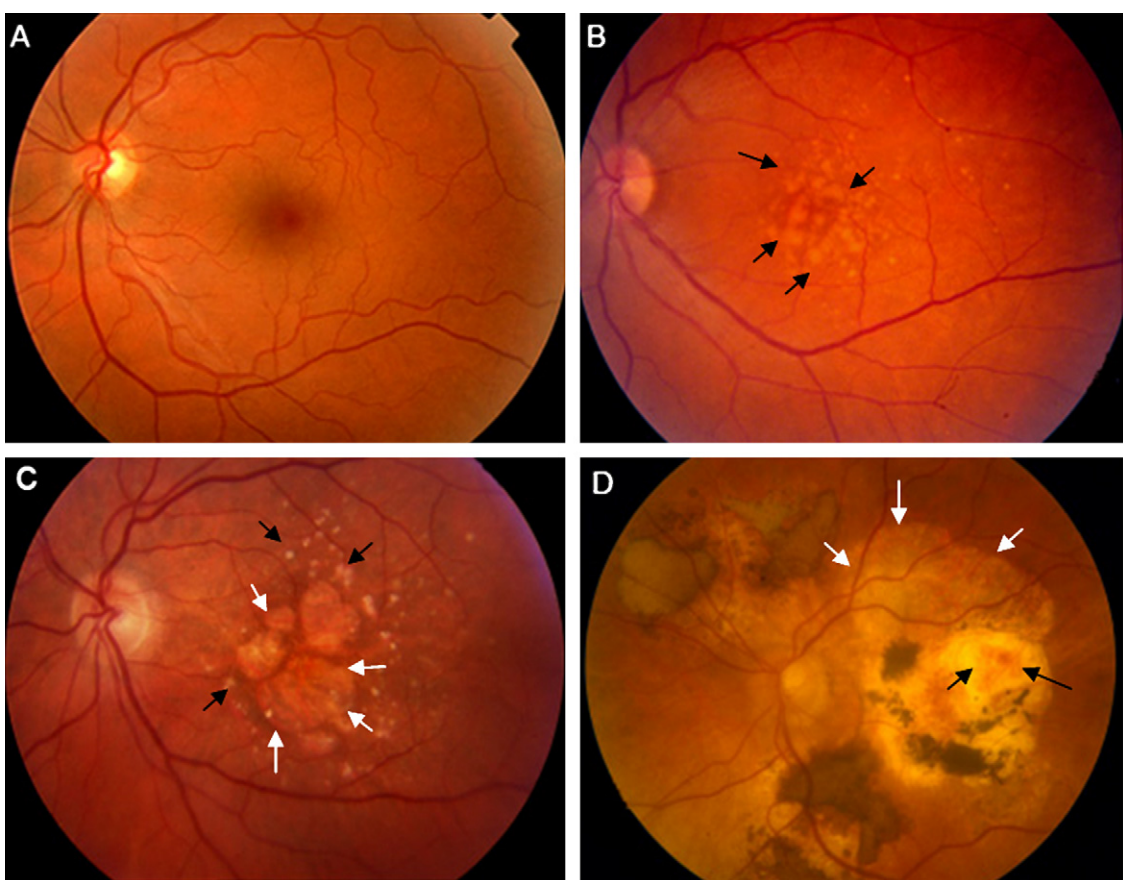

Fig. 1. Fundus photography of normal control (A) and AMD cases (B–D) identified in Utah Population Database. A, normal control; B, confluent soft drusen (black arrow); C, geographic atrophy (white arrow) and soft drusen (black arrow); D, choroidal neovascularization (black arrow) and atrophy (white arrow).

nor.state.ut.us/dea). In addition, many environmental factors are less prevalent in the state as compared to the rest of the U.S. population. For example, the CDC Behavioral Risk Factor Surveillance System reports that Utah has one of the lowest alcohol consumption rates in the nation and the lowest tobacco consumption rate at 9.8% (http://www.cdc.gov/brfss/). Large family size, minimization of environmental factors shown to be associated with AMD such as smoking (Klein, Klein, & Moss, 1998) and alcohol consumption (Klein, Klein, Tomany, & Moss, 2002), as well as the copious data available from the UPDB makes the Utah community a unique and useful group to study.

This study attempts to demonstrate the familial aggregation of AMD using the UPDB, a University of Utah research resource that represents over 6 million individuals and covers a period from the late 1700s to the present. In this study, we identified extensive AMD pedigrees in Utah and calculated AMD risk in parents, siblings, first cousins, and second cousins, which enabled us to evaluate the population-attributable risk (PAR) in this unique population.

2. Methods

2.1. Study design

This is a population-based cross-sectional and case-control study using data from the UPDB. The UPDB includes data from the Family History Library maintained by the Church of Jesus Christ of Latter-day Saints (LDS), vital records from the Utah State Department of Health, and other statewide data sets (http://www.hci.utah.edu/groups/ppr/data.html). The resource includes family history data on approximately 4 million individuals, representing pedigrees that span up to 11 generations. The majority of families living in Utah are represented in this database with a special emphasis on genealogy records of the founders of Utah and their descendants (Skolnick, Bean, & Dintelman, 1979).

Beginning in 2003, a link between medical information contained in the University of Utah Health Sciences Center (UUHSC) and family history information in the UPDB was established to facilitate studies of the familiality of a broad range of diseases. The UUHSC contains more than 1.5 million patient demographic records and includes medical information on both in-patient and out-patient records. Over one million (74%) patients have been matched to a "person record" in the UPDB. The extensive family histories available in the UPDB, combined with information from UUHSC medical records and statewide vital records, allow for the identification of large pedigrees and calculation of population-based risks of diseases such as AMD. The following results emphasize the valuable resources available for identifying AMD genes for this study.

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).

2.2. AMD cases

UUHSC hospital and clinic records were searched to identify patients with varying severities of AMD, classified by ICD9 codes. ICD9 codes 362.50, 362.51 and 362.52 were used to code for senile macular degeneration, unspecified, nonexudative senile macular degeneration, and exudative senile macular degeneration, respectively. A total of 4764 patients were identified. Only patients with at least one parent or one child in the UPDB were used for further familial statistical assessments. Most of the family information was drawn from the genealogy records of Utah founder families indicating that, there is a limited number of subjects with relatives in the database. From these results, 2772 records (58%) had sufficient family information in the UPDB to be included in the PAR and relative risk (RR) analyses.

2.3. Population controls

After identifying AMD cases, controls were selected from the linked UUHSC-UPDB cohort. Only controls with family information recorded in the UPDB were used. Controls were also matched to cases by gender and birth year ±2.5 years, presence in the linked UPDB-UUHSC set (1,072,860 patients), and absence of AMD diagnosis. One control was picked per case, and controls were not reused.

2.4. Statistical analyses

2.4.1. 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 and weighting the contribution of each relative by the probability that the relative shares an allele with the subject by common descent. Boucher and Kerber (2001) describe an empirical Bayes adjustment for measurement error.

2.4.2. Population-attributable risk

PAR was calculated using a conditional logistic regression method as 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 (PAC) for each case are computed where PAC = (RR − 1)/RR, where RR is the relative risk estimated from the model for the observed level of FSIR. The PAR is calculated as the mean PAC across all the cases.

2.4.3. Relative risks

RRs for parents, siblings, and first and second cousins of the 2772 cases were also calculated using unconditional logistic regression, following the method described by Bai, Sherman, Khoury, and Flanders (2000).

2.4.4. 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 $X > x$ given an expected number, μ.

3. Results

The identified population of AMD cases and matched controls were utilized to calculate various risks of disease development, demonstrating familial risk of AMD. These risks include the proportion of disease in the population attributable to familial factors, or PAR, as well as the recurrent risks among family members related to patients who have a diagnosis of AMD. RRs were broken down to specific familial relation to the affected cases.

Using data from conditional logistic regression computations the raw PAR for AMD was calculated to be 0.22 (95% CI 0.16–0.27), and the adjusted PAR was 0.34 (95% CI 0.25–0.41). Increased RR was found in siblings, first cousins, second cousins, and parents of affected cases, as displayed in Table 1 (with 95% confidence intervals).

Identification of 16 large pedigrees containing at least five or more affected family members, having a p value

Table 1
Number of cases, controls, and relative risk of individuals with different relationships to probands for AMD

Relationship	Cases ($n = 2772$)		Controls ($n = 2772$)		Relative risk (95% CI)	p value
	Affected	Unaffected	Affected	Unaffected		
Parent	70(2.22%)	3088(97.78%)	10(0.41%)	2408(99.59%)	5.66(2.89–11.08)	4.33×10^{-07}
Sibling	199(9.69%)	1855(90.31%)	60(3.48%)	1664(96.52%)	2.95(2.19–3.97)	9.40×10^{-13}
First cousin	349(3.60%)	9332(96.40%)	260(2.78%)	9093(97.22%)	1.29(1.10–1.52)	.002011
Second cousin	1687(3.12%)	52464(96.88%)	1410(2.68%)	51282(97.32%)	1.13(1.05–1.22)	.000689

$<.05$ and an increased FSIR further emphasized the familial aggregation of AMD in the Utah population. The kinship analysis software provided a founder Person ID for each family, number of descendents, observed number of affected individuals, expected number of affected individuals, 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 with careful manual analysis of each affected case identified in the clusters. Large pedigrees were drawn out using Peddraw software, and the results are shown in Fig. 2.

There were 28 families identified having five or more living affected members within each family. For each of these families the p value under the null hypothesis of no familial disease aggregation is .05 or less and the FSIR value is 1.5 or higher. The family members within these pedigrees were compared. They reduced to 16 extended large families. In some instances more than one founder was identified for the same group of cases. This is annotated in Table 2 with the cluster number followed by a letter corresponding to the different founder. The number of descendents in each family ranged between 38 and 8231 members, and FSIRs for each family ranged from 1.90 to 214, as shown in Table 2. The median number of descendents in each pedigree was 1365 and the median FSIR was 3.95, demonstrating a strong familial aggregation of AMD in Utah families. Thus the linked UPDB-UUHSC records and kinship analysis software provides the basis to identify and recruit extended families with clustering of AMD.

4. Discussion

AMD risk can be significantly attributed to genetic factors, and this study confirms that AMD aggregates in Utah families. The range in FSIR further demonstrates the multi-factorial nature of AMD. Environmental data such as diet and smoking history is not available directly from the UPDB. However, this data could be collected during patient interviews and may prove to further enhance single-family studies. The adjusted PAR for AMD using the UPDB was found to be 34%. This is consistent with popu-

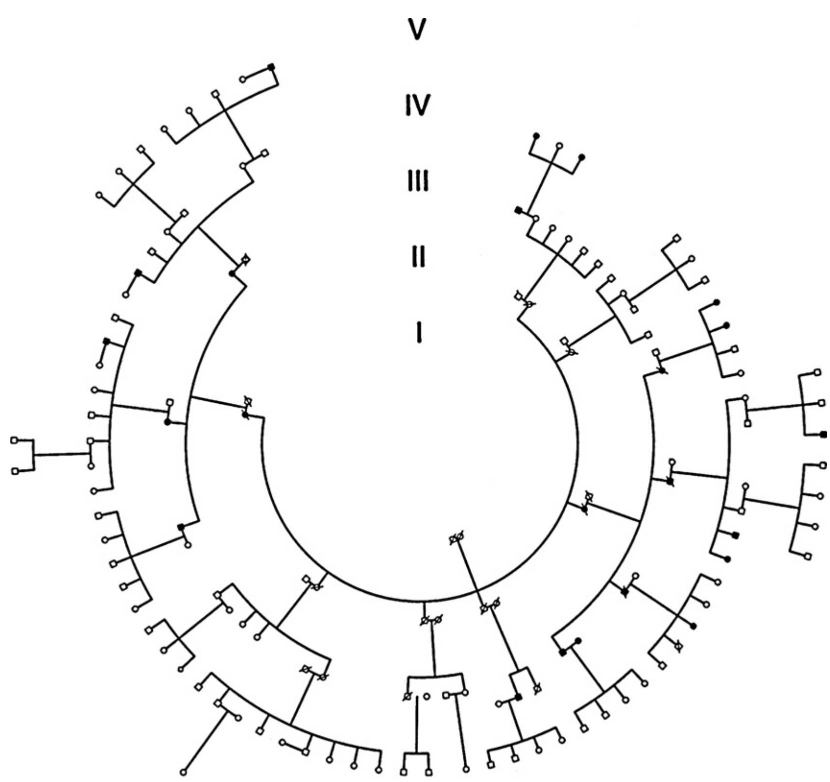

Fig. 2. Pedigree (cluster #6) identified from Utah Population Database containing 16 living AMD cases.

Table 2
Sixteen families identified from Utah Population Database

Cluster	Descendants	Observed	Expected	FSIR	*p* value
1a	1238	5	1.2519	3.9939	.0092
1b	2044	7	2.1032	3.3283	.0059
2	1725	5	1.6904	2.9578	.029
3a	468	8	0.4015	19.9239	0
3b	182	7	0.2077	33.7044	0
3c	107	7	0.0889	78.7024	0
3d	373	7	0.4678	14.9622	0
3e	38	7	0.0326	214.4589	0
4	3670	6	2.4634	2.4357	.0396
5	2934	7	3.1483	2.2235	.0415
6a	2911	6	1.7249	3.4784	.0086
6b	8231	11	5.8038	1.8953	.035
7a	1327	5	1.2754	3.9203	.0099
7b	1404	5	1.4638	3.4157	.0169
8	1181	5	0.8854	5.6474	.0022
9	1677	6	1.6042	3.7402	.0061
10a	1685	6	1.427	4.2046	.0035
10b	1998	7	1.6882	4.1463	.0018
11a	935	5	0.7177	6.9663	.0009
11b	390	5	0.445	11.2355	.0001
11c	790	6	0.7226	8.3029	.0001
11d	380	6	0.4147	14.4698	0
12	2212	7	2.0202	3.465	.0048
13	1271	5	1.2963	3.8573	.0105
14	3234	9	2.6379	3.4118	.0016
15	2358	5	1.9638	2.546	.0494
16a	4177	8	2.4293	3.2931	.0036
16b	605	5	0.5624	8.8907	.0003

lation-based and twin studies which have estimated an attributable risk of anywhere from 42% to 76% (Grizzard, Arnett, & Haag, 2003; Hammond et al., 2002; Klaver et al., 1998; Klein, Mauldin, & Stoumbos, 1994; Meyers, 1994; Seddon et al., 1997, 2005). Our estimates may be somewhat conservative as AMD cases may be underdiagnosed due to the assumption of unaffected status when there was no AMD diagnosis given in the UUHSC system, as the UUHSC is only one of many medical care options in the Utah state. Another possible limitation of our study is that data was only available on 58% of those with AMD. The UPDB is currently working with other health care providers throughout the state to incorporate their medical records into this database. This would help further delineate AMD status in our population. This is an ongoing study, and we plan to re-assess this population periodically in the future in order to incorporate new diagnostic information. A future direction of this study will include more specific ICD9 code stratification to assess only advanced AMD and correlate this risk of vision loss from AMD.

While several population-based studies have demonstrated familial aggregation of AMD (Heiba et al., 1994; Klaver et al., 1998; Klein et al., 2001; Seddon et al., 1997), this is the first study to show relative risks of second cousins. Studies of second cousins may provide a more impartial estimate of familial aggregation of AMD by further reducing various environmental bias such as diet, smoking, and alcohol consumption. A particularly interesting observation in this study was the relative risk of second cousins (1.13) when compared with the percentage of shared alleles (2%). Additionally, in today's age of available information and better understanding of genetic influence on common diseases, questions regarding risk and prevention of disease are often posed in the clinical setting. The recent discovery of the CFH and HTRA1 alleles associated with AMD has appeared in mainstream news sources, and often patients inquire as to their odds of developing AMD based on both family history and genetic testing availability. Common disease predisposition genes identified in Utah are represented similarly in other U.S. and international studies in terms of frequency and penetrance. Relative risks for cancer and other diseases calculated for this population are comparable to published estimates for other populations (Goldgar, Easton, Cannon-Albright, & Skolnick, 1994). The Utah population is biologically representative of a broad spectrum of the Caucasian U.S. population and is genetically similar to other Northern European-derived populations. The Utah population has a low consanguinity rate that is very similar to that of the U.S. population due to a large founding population and high rates of immigration from a diverse group of outside populations (Jorde, 1989; McLellan, Jorde, & Skolnick, 1984). Therefore, we feel that the relative risk calculations based on UPDB data can reasonably be extended to other communities.

The extensive AMD pedigrees identified in this study can aid in further understanding the genetics and pathogenesis of AMD. Blood samples and phenotypic data have been collected on several members of these large pedigrees and the value of these pedigrees may become even more apparent with recent genetic discoveries. The possibility of underlying genetic heterogeneity for disease often lessens enthusiasm for linkage studies. In the face of genetic heterogeneity represented by multiple genes for a single disorder, the importance of extended pedigrees with large numbers of affected patients becomes apparent. A small number of large, independently informative pedigrees, such as the ones identified in this study, may also help to define new linked regions for AMD and provide more clarity and narrower regions in currently identified loci. The approach to localization and isolation of predisposition genes using a population-based genealogy and a population-based registry of affected individuals has been successful in Utah in the localization and/or cloning of many disease genes in diseases such as p16 in melanoma (Berthelemy-Okazaki et al., 2005; Kamb et al., 1994) and the two hereditary breast cancer genes BRCA1 (Miki et al., 1994) and BRCA2 (Tavtigian et al., 1996, 2001; Wooster et al., 1994).

The combination of PAR findings, RR calculations, and cluster analysis demonstrates familial aggregation of AMD in the Utah population. The UPDB is a powerful tool to identify familial risk and large pedigrees with several affected members of AMD, and future use of the database may aid in findings in other common eye diseases such as glaucoma and diabetic retinopathy. These pedigrees and risk assessments of the Utah population have broad clinical applications and may help play an important role in understanding the pathogenesis and progression of AMD.

Acknowledgments

Partial support for all data sets within UPDB is being provided by the Huntsman Cancer Institute, with special thanks to Richard Pimentel and Richard Kerber. We also to acknowledge the grants from the National Institutes of Health, Foundation Fighting Blindness, the Ruth and Milton Steinbach Fund, Ronald McDonald House Charities, Knights Templar Eye Research Foundation, Grant Ritter Fund, American Health Assistance Foundation, the Karl Kirchgessner Foundation, Children's Health Research Center, Val and Edith Green foundation and the Simmons Foundation. Dr. Zhang is a Lew Wasserman Merit Award scholar of Research to Prevent Blindness (RPB).

References

Bai, Y., Sherman, S., Khoury, M. J., & Flanders, W. D. (2000). Bias associated with study protocols in epidemiologic studies of disease familial aggregation. *American Journal of Epidemiology, 151*, 927–937.

Bean, L., Mineau, G., & Anderton, D. (1990). *Fertility change on the American frontier: Adaptation and innovation*. Berkeley: University of California Press.

Berthelemy-Okazaki, N., Zhao, Y., Yang, Z., Camp, N. J., Farnham, J., Parker, D., et al. (2005). Examination of ELN as a candidate gene in the Utah intracranial aneurysm pedigrees. *Stroke, 36*, 1283–1284.

Boucher, K. M., & Kerber, R. A. (2001). Measures of familial aggregation as predictors of breast-cancer risk. *Journal of Epidemiology and Biostatistics, 6*, 377–385.

Bruzzi, P., Green, S. B., Byar, D. P., Brinton, L. A., & Schairer, C. (1985). Estimating the population attributable risk for multiple risk factors using case-control data. *American Journal of Epidemiology, 122*, 904–914.

Cameron, D. J., Yang, Z., Gibbs, D., Chen, H., Kaminoh, Y., Jorgensen, A., et al. (2007). HTRA1 variant confers similar risks to geographic atrophy and neovascular age-related macular degeneration. *Cell Cycle, 6*, 1122–1125.

Dewan, A., Liu, M., Hartman, S., Zhang, S. S., Liu, D. T., Zhao, C., et al. (2006). HTRA1 promoter polymorphism in wet age-related macular degeneration. *Science, 314*, 989–992.

Edwards, A. O., Ritter, R., 3rd, Abel, K. J., Manning, A., Panhuysen, C., & Farrer, L. A. (2005). Complement factor H polymorphism and age-related macular degeneration. *Science, 308*, 421–424.

Friedman, D. S., O'Colmain, B. J., Munoz, B., Tomany, S. C., McCarty, C., de Jong, P. T., et al. (2004). Prevalence of age-related macular degeneration in the United States. *Archives of Ophthalmology, 122*, 564–572.

Goldgar, D. E., Easton, D. F., Cannon-Albright, L. A., & Skolnick, M. H. (1994). Systematic population-based assessment of cancer risk in first-degree relatives of cancer probands. *Journal of the National Cancer Institute, 86*, 1600–1608.

Grizzard, S. W., Arnett, D., & Haag, S. L. (2003). Twin study of age-related macular degeneration. *Ophthalmic Epidemiology, 10*, 315–322.

Hageman, G. S., Anderson, D. H., Johnson, L. V., Hancox, L. S., Taiber, A. J., Hardisty, L. I., et al. (2005). A common haplotype in the complement regulatory gene factor H (HF1/CFH) predisposes individuals to age-related macular degeneration. *Proceedings of the National Academy of Sciences of the United States of America, 102*, 7227–7232.

Hageman, G. S., Luthert, P. J., Victor Chong, N. H., Johnson, L. V., Anderson, D. H., & Mullins, R. F. (2001). An integrated hypothesis that considers drusen as biomarkers of immune-mediated processes at the RPE-Bruch's membrane interface in aging and age-related macular degeneration. *Progress in Retina and Eye Research, 20*, 705–732.

Haines, J. L., Hauser, M. A., Schmidt, S., Scott, W. K., Olson, L. M., Gallins, P., et al. (2005). Complement factor H variant increases the risk of age-related macular degeneration. *Science, 308*, 419–421.

Hammond, C. J., Webster, A. R., Snieder, H., Bird, A. C., Gilbert, C. E., & Spector, T. D. (2002). Genetic influence on early age-related maculopathy: A twin study. *Ophthalmology, 109*, 730–736.

Heiba, I. M., Elston, R. C., Klein, B. E., & Klein, R. (1994). Sibling correlations and segregation analysis of age-related maculopathy: The Beaver Dam Eye Study. *Genetic Epidemiology, 11*, 51–67.

Jorde, L. B. (1989). Inbreeding in the Utah Mormons: An evaluation of estimates based on pedigrees, isonymy, and migration matrices. *Annals of Human Genetics, 53*, 339–355.

Kamb, A., Shattuck-Eidens, D., Eeles, R., Liu, Q., Gruis, N. A., Ding, W., et al. (1994). Analysis of the p16 gene (CDKN2) as a candidate for the chromosome 9p melanoma susceptibility locus. *Nature Genetics, 8*, 23–26.

Kaplan, H. J., Leibole, M. A., Tezel, T., & Ferguson, T. A. (1999). Fas ligand (CD95 ligand) controls angiogenesis beneath the retina. *Nature Medicine, 5*, 292–297.

Kerber, R. A. (1995). Method for calculating risk associated with family history of a disease. *Genetic Epidemiology, 12*, 291–301.

Klaver, C. C., Wolfs, R. C., Assink, J. J., van Duijn, C. M., Hofman, A., & de Jong, P. T. (1998). Genetic risk of age-related maculopathy. Population-based familial aggregation study. *Archives of Ophthalmology, 116*, 1646–1651.

Klein, M. L., Mauldin, W. M., & Stoumbos, V. D. (1994). Heredity and age-related macular degeneration. Observations in monozygotic twins. *Archives of Ophthalmology, 112*, 932–937.

Klein, R., Klein, B. E., & Linton, K. L. (1992). Prevalence of age-related maculopathy. The Beaver Dam Eye Study. *Ophthalmology, 99*, 933–943.

Klein, R., Klein, B. E., & Moss, S. E. (1998). Relation of smoking to the incidence of age-related maculopathy. The Beaver Dam Eye Study. *American Journal of Epidemiology, 147*, 103–110.

Klein, B. E., Klein, R., Lee, K. E., Moore, E. L., & Danforth, L. (2001). Risk of incident age-related eye diseases in people with an affected sibling: The Beaver Dam Eye Study. *American Journal of Epidemiology, 154*, 207–211.

Klein, R., Klein, B. E., Tomany, S. C., & Moss, S. E. (2002). Ten-year incidence of age-related maculopathy and smoking and drinking: The Beaver Dam Eye Study. *American Journal of Epidemiology, 156*, 589–598.

Klein, R. J., Zeiss, C., Chew, E. Y., Tsai, J. Y., Sackler, R. S., Haynes, C., et al. (2005). Complement factor H polymorphism in age-related macular degeneration. *Science*.

Krzystolik, M. G., Afshari, M. A., Adamis, A. P., Gaudreault, J., Gragoudas, E. S., Michaud, N. A., et al. (2002). Prevention of experimental choroidal neovascularization with intravitreal anti-vascular endothelial growth factor antibody fragment. *Archives of Ophthalmology, 120*, 338–346.

McLellan, T., Jorde, L. B., & Skolnick, M. H. (1984). Genetic distances between the Utah Mormons and related populations. *American Journal of Human Genetics, 36*, 836–857.

Meyers, S. M. (1994). A twin study on age-related macular degeneration. *Transactions of the American Ophthalmological Society, 92*, 775–843.

Meyers, S. M., Greene, T., & Gutman, F. A. (1995). A twin study of age-related macular degeneration. *American Journal of Ophthalmology, 120*, 757–766.

Miki, Y., Swensen, J., Shattuck-Eidens, D., Futreal, P. A., Harshman, K., Tavtigian, S., et al. (1994). A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. *Science, 266*, 66–71.

Okamoto, N., Tobe, T., Hackett, S. F., Ozaki, H., Vinores, M. A., LaRochelle, W., et al. (1997). Transgenic mice with increased expression of vascular endothelial growth factor in the retina: A new model of intraretinal and subretinal neovascularization. *American Journal of Pathology, 151*, 281–291.

Penfold, P. L., Killingsworth, M. C., & Sarks, S. H. (1985). Senile macular degeneration: The involvement of immunocompetent cells. *Graefe's Archive for Clinical and Experimental Ophthalmology, 223*, 69–76.

Seddon, J. M., Ajani, U. A., & Mitchell, B. D. (1997). Familial aggregation of age-related maculopathy. *American Journal of Ophthalmology, 123*, 199–206.

Seddon, J. M., Cote, J., Page, W. F., Aggen, S. H., & Neale, M. C. (2005). The US twin study of age-related macular degeneration: Relative roles of genetic and environmental influences. *Archives of Ophthalmology, 123*, 321–327.

Skolnick, M., Bean, L., Dintelman, S., & Mineau, G. (1979). A computerized family history database system. *Social Science Research, 63*, 506–523.

Smith, W., Assink, J., Klein, R., Mitchell, P., Klaver, C. C., Klein, B. E., et al. (2001). Risk factors for age-related macular degeneration: Pooled findings from three continents. *Ophthalmology, 108*, 697–704.

Tavtigian, S. V., Simard, J., Rommens, J., Couch, F., Shattuck-Eidens, D., Neuhausen, S., et al. (1996). The complete BRCA2 gene and mutations in chromosome 13q-linked kindreds. *Nature Genetics, 12*, 333–337.

Tavtigian, S. V., Simard, J., Teng, D. H., Abtin, V., Baumgard, M., Beck, A., et al. (2001). A candidate prostate cancer susceptibility gene at chromosome 17p. *Nature Genetics, 27*, 172–180.

van Leeuwen, R., Klaver, C. C., Vingerling, J. R., Hofman, A., & de Jong, P. T. (2003). Epidemiology of age-related maculopathy: A review. *European Journal of Epidemiology, 18*, 845–854.

Vingerling, J. R., Dielemans, I., Hofman, A., Grobbee, D. E., Hijmering, M., Kramer, C. F., et al. (1995). The prevalence of age-related maculopathy in the Rotterdam Study. *Ophthalmology, 102*, 205–210.

Wooster, R., Neuhausen, S. L., Mangion, J., Quirk, Y., Ford, D., Collins, N., et al. (1994). Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q12-13. *Science, 265*, 2088–2090.

Wylie, J. E., & Mineau, G. P. (2003). Biomedical databases: Protecting privacy and promoting research. *Trends in Biotechnology, 21*, 113–116.

Yang, Z., Camp, N. J., Sun, H., Tong, Z., Gibbs, D., Cameron, D. J., et al. (2006). A variant of the HTRA1 gene increases susceptibility to age-related macular degeneration. *Science, 314*, 992–993.

Zareparsi, S., Branham, K. E., Li, M., Shah, S., Klein, R. J., Ott, J., et al. (2005). Strong association of the Y402H variant in complement factor H at 1q32 with susceptibility to age-related macular degeneration. *American Journal of Human Genetics, 77*, 149–153.