Glaucoma and Genomic Medicine

Research is bringing clinicians closer to personalized treatment based on risk alleles and the interaction with biological networks and environmental factors.

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Since Pratap Challa, MD, wrote about genetics and glaucoma for *Glaucoma Today* in 2003,[1] investigators have expanded previously successful research to identify more genes associated with this potentially blinding disease. This article updates the ongoing search for genetic markers for glaucoma and genes that contribute to the disease's onset and progression, discusses the shift from a single-gene to a complex disease model, and suggests how genomic testing may help clinicians develop personalized treatments for their patients in the future.

IDENTIFYING GENETIC MARKERS

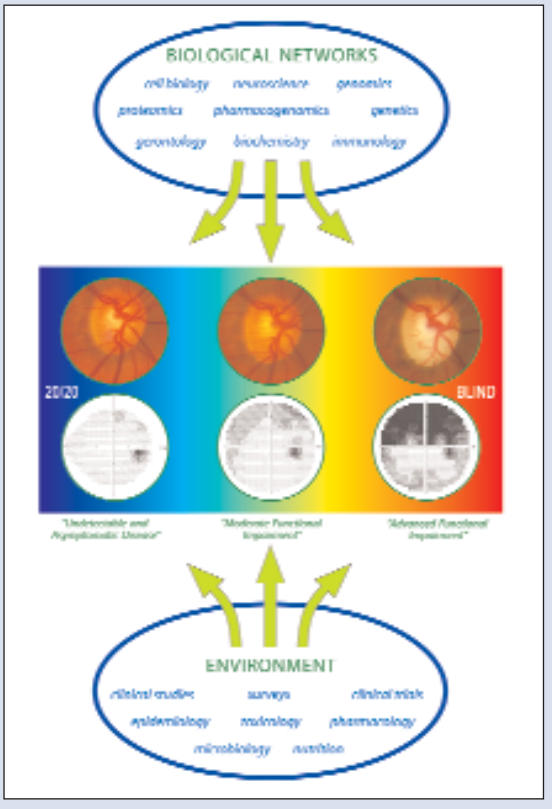
Traditionally, researchers have collaborated with patients, members of patients' families, clinicians, and geneticists to identify genetic markers for diseases. This approach has led to the identification of 70 genes, chromosomal regions containing genes (ie, loci), and alleles that either cause glaucoma or are associated with syndromes encompassing glaucoma (Table 1). The highly penetrant forms of glaucoma associated with these genes include infantile-onset, juvenile-onset, and syndromic glaucoma as well as a very

THE COMPLEX DISEASE MODEL OF GLAUCOMA

A 68-year-old woman was initially diagnosed with glaucoma based on the appearance of her neuroretinal rim (left), which violated the ISNT rule.[1] At the time of diagnosis, her IOPs measured 33 mm Hg OU, and her pachymetry was 584 µm OD and 566 µm OS. The patient was otherwise asymptomatic.

Although the patient's IOPs fluctuated between 7 and 13 mm Hg with medical and surgical treatment, she developed progressive cupping of the optic disc and visual field loss (center and right) over time.[2]

A better understanding of how biological (top oval) and environmental (bottom oval) factors influence genetic markers that affect the severity of glaucoma and the patient's response to treatment might have helped us design a more effective course of therapy for this patient. Adopting a complex model of glaucoma could also lead to customized interventions for different stages of disease or the development novel treatments based stem cells, gene therapy, and nanotechnology.



1. Jonas JB, Dichtl A. Evaluation of the retinal nerve fiber layer. *Surv Ophthalmol.* 1996;40:369-378.
2. Weinreb RN, Friedman DS, Fechtner RD, et al. Risk assessment in the management of patients with ocular hypertension. *Am J Ophthalmol.* 2004;138:458-467.

small proportion of the high- and normal-pressure glaucomas. These forms of the disease, however, account for only a small fraction of all the glaucomas that occur.

Studies have also identified loci that affect an individual's potential susceptibility to glaucoma[2-5] or influence the severity of the disease.[6-8] The "single gene, single disease" hypothesis assumes that the presence or absence of a mutation dictates whether a patient will or will not have disease. This approach, however, fails to identify genetic variations (risk alleles) that influence an individual's likelihood of developing glaucoma, the rate of the disease's progression, and how patients respond to treatment. Clearly, we need to shift from a simple monogenic to a complex multigenic model if we want to understand the genetic complexity of glaucoma[2,9] (see *The Complex Disease Model of Glaucoma*).

TABLE 1. GENES AND LOCI ASSOCIATED WITH GLAUCOMA AND GLAUCOMA-RELATED SYNDROMES

Chromosome location	Gene [Locus]	Glaucoma phenotype
1p36.3-p36.2	PLOD	Ehlers-Danlos syndrome VI
1p36.2-p36.1	[GLC3B]	Infantile glaucoma, type B
1p34.1	POMGNT1	Muscle-eye-brain disease
1p34.3-p32.3	COL8A2	Posterior polymorphous corneal dystrophy 2, Fuchs endothelial corneal dystrophy
1p21	COL11A1	Marshall syndrome, Stickler syndrome II
1q23-q24	MYOC	Juvenile open-angle glaucoma
2p22.2	CYP1B1	Infantile glaucoma, Peter anomaly
2p16.3-p15	[GLC1H]	High-tension open-angle glaucoma
2q1-q13	[GLC1B]	High-tension open-angle glaucoma
3p22-p21	[GLC1L]	Open-angle glaucoma
3q21-q24	[GLC1C]	High-tension open-angle glaucoma
3q28-q29	OPA1	Optic nerve atrophy, normal-tension open-angle glaucoma
4p16.3	IDUA	Hurler syndrome, mucopolysaccharidosis type IH
4q21	SLC4A4	Renal tubular acidosis, mental retardation, glaucoma
4q25-q26	PITX2	Iridogoniodysgenesis 2 or Rieger type 1, Peter anomaly, ring dermoid of cornea
5q11-q13	ARSB	Mucopolysaccharidosis VI
5q12-q14	VCAN	Wagner syndrome
5q21.2	WDR36	High- and normal-tension open-angle glaucoma
5q22.1-q32	[GLC1M]	Open-angle glaucoma
5q22-q24	[GLC1N]	Open-angle glaucoma
6p21.3	COL11A2	Stickler syndrome II, Weissenbacher-Zweymüller syndrome
6p25	FOXC1	Iridogoniodysgenesis 1, Peter anomaly
6q21-q23.2	GJA1	Oculodentodigital dysplasia, microphthalmia
7q35-q36	(GLC1F)	High-tension open-angle glaucoma
7q35-q36	[GPDS1]	Pigment dispersion 1
8q22.3	[KTS]	Klippel-Trenaunay-Weber syndrome
8q23	[GLC1D]	High-tension open-angle glaucoma
9p24.3-p23	GLIS3	Neonatal diabetes mellitus and hypothyroidism, infantile glaucoma
9q22	[GLC1J]	Juvenile-onset open-angle glaucoma 2
9q22.1-q31	PTCH1	Basal cell nevus syndrome
9q33.3	LMX1B	Nail-patella syndrome
10p14	OPTN	Normal-tension open-angle glaucoma
10p11.22	ZEB1	Posterior polymorphous corneal dystrophy 3
10q24.31	PAX2	Renal-coloboma syndrome, "morning glory" optic nerve
10q24.32	PITX3	Anterior segment dysgenesis

GENETIC AND ENVIRONMENTAL INTERACTIONS IN GLAUCOMA

The complex genetic model of glaucoma focuses on "nature via nurture,"[10] the process by which interactions between biological networks (nature) and the environment (nurture) influence a disease's clinical features and risk factors. These interactions can have variable effects along a disease's continuum depending on when they occur during an individual's life (ie, embryogenesis, organogenesis, development, and senescence).

In complex models of disease, some measurable clinical risk factors are quantitative traits. A well-known and frequently studied quantitative trait of glaucoma is IOP.[11-16] Familial studies have demonstrated a high correlation[17] and concordance[18] between IOP within families. In addition, population studies have shown that IOP is heritable based

TABLE 1. GENES AND LOCI ASSOCIATED WITH GLAUCOMA AND GLAUCOMA-RELATED SYNDROMES (*CONTINUED*)

Chromosome location	Gene [Locus]	Glaucoma phenotype
11p13	PAX6	Aniridia, Peter anomaly
11p15	SBF2	Charcot-Marie-Tooth disease type 4B with juvenile-onset open-angle glaucoma
11p13	[NNO1]	Nanophthlamos
11q23.1	MFRP	Nanophthalmos
11q23.3	C1QTNF5	Late-onset retinal degeneration and long anterior zonules
11q13.4	LRP5	Osteogenesis imperfecta, ocular form
12q12-q13.2	COL2A1	Stickler syndrome I
13q14	[RIEG2]	Rieger 2
13q31-q32	[MCOR]	Congenital microcoria
14q23.1	SIX6	Microphthalmia with cataract 2
14q24	POMT2	Walker-Warburg syndrome
14q24.3	VSX2	Microphthalmos
14q32	[MCOP1]	Microphthalmos
15q11-q13	[GLC1I]	High-tension open-angle glaucoma
15q21.1	FBN1	Weill-Marchesani syndrome, ectopia lentis, Marfan syndrome
15q24-q25	LOXL1	Risk allele for pseudoexfoliation glaucoma[19]
15q22-q24	[GLC1N]	Juvenile-onset open-angle glaucoma
16p13.3	CREBBP	Rubinstein syndrome
17q11.2	NF1	Neurofibromatosis 1
18q11-q21	(GPDS2)	Pigment dispersion
18q21.31	RAX	Microphthalmos
19p13.3	ADAMTS10	Weill-Marchesani syndrome
19q34.1	POMT1	Walker-Warburg syndrome
19q31-q33	FCMD	Walker-Warburg syndrome
19q13.3	FKRP	Walker-Warburg syndrome
20p12	[GLC1K]	Juvenile-onset open-angle glaucoma 3
20p11.21	VSX1	Posterior polymorphous corneal dystrophy 1
21q22.3	CBS	Homocystinuria, ectopia lentis
22q12.2	NF2	Neurofibromatosis 2
22q12.3-q13.1	LARGE	Walker-Warburg syndrome
Xp11.4	NPD	Coats' disease, uveitis, secondary glaucoma
Xp11.4	BCOR	Microphthalmia, syndromic 2
Xp22	HCCS	Microphthalmia, syndromic 7
Xq25	OCRL	Lowe oculocerebrorenal syndrome
Xq28	—	Armfield X-linked mental retardation syndrome

on familial relationships,[20-22] and researchers have identified several loci (by genome-wide association methods)[23-26] for higher IOP.

The link between genetics and IOP is not simple, however, because IOP is a complex trait determined by the production of aqueous humor, uveoscleral and trabecular outflow, and episcleral venous pressure. Recently, our colleagues and demonstrated that individuals who have a higher flow of aqueous humor in the morning also have a relatively higher flow at night. These same individuals, however, still maintain a normal circadian rhythm of decreased flow at night. The finding of individual concordance has direct implications for fluctuations in IOP (a known risk factor for glaucomatous progression).[27]

The challenges we researchers must overcome to expand our knowledge of the genetic basis of glaucoma include (1) adopting a complex disease model and (2) designing and implementing studies that can help us develop personalized treatments.

A greater understanding of glaucoma will no doubt lead to new tests[28] that will help us diagnose specific types of the disease and provide more information about its clinical course and prognosis. We could also benefit from tests that identify risk factors, genetic modifiers, and markers that affect individuals' responses to specific treatments (ie, efficacy and unwanted side effects).

APPLIED GENOMICS

Despite the lessons we have learned from clinical trials[11-16] as well as a growing understanding of ocular genomics, pharmacology, and the dynamics of aqueous humor, glaucoma continues to blind patients.[29,30] We therefore need to improve our ability to detect and treat the disease[31] and to expand patients' access to healthcare. Genomics may help us to achieve these goals by facilitating the development of personalized medical treatments.

For the past few years, oncologists have used personalized therapy to improve the early detection and treatment of certain types of breast cancer.[32] Their success is the direct result of an interdisciplinary assault that comprised population-based studies, clinical resources, and the translation of basic research into clinical strategies.

Ocular medicine is at the cusp of a similar shift toward personalized therapies. Some novel treatments include antivascular endothelial growth factors,[33] gene replacement for specific inherited dystrophies,[34] and the delivery of targeted growth factors with encapsulated cell technology.[35]

Approximately 50% of cases of age-related macular degeneration are attributed to single nucleotide polymorphisms in the complement factor H (CFH),[36] *LOC387715*,[37] component 2,[38] factor B,[38] and *HTRA1*[39] genes. Investigators have also identified environmental factors that appear to offer protection against (eg, the use of specific micronutrients[40,41]) or contribute to (eg, smoking[42,43] and increased body mass index[43]) the disease's progression. Based on these discoveries, ophthalmologists have begun to recommend individualized treatments for certain retinal diseases and to advise patients how they can modify their behavior to

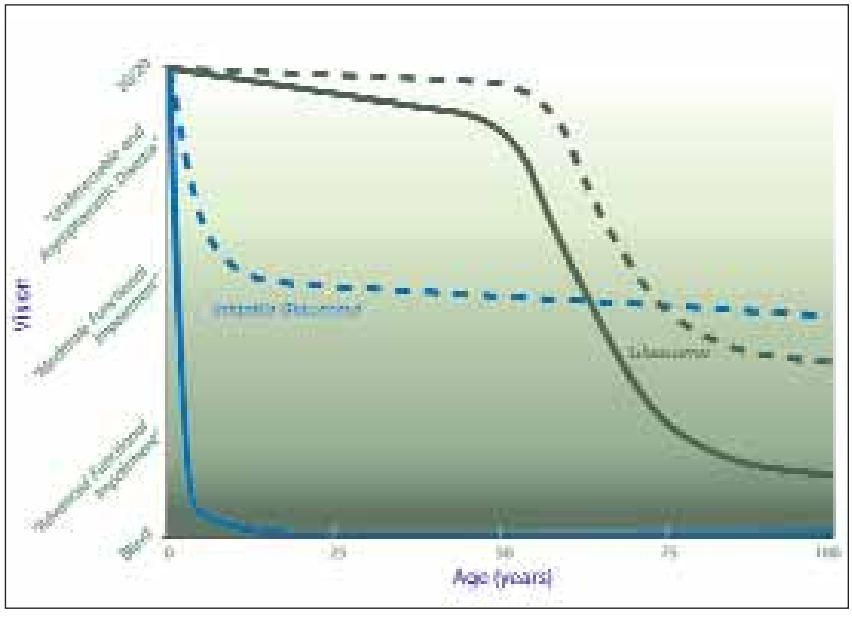


Figure 1. The diagram shows levels of visual impairment along the continuum of glaucoma, which ranges from undetectable and asymptomatic disease (white background) to blindness (dark green background). The solid blue line represents the average progression of infantile glaucoma. This condition can rapidly result in blindness if patients do not receive treatment early in life. The dashed blue line represents the average result of surgical treatment for glaucoma (based on greater than a 0.4 decimal equivalent visual acuity outcome [20/50]).[44-49] The causes of poor visual outcomes after surgery include intra- or postoperative complications, multiple failed procedures, and anisometropic amblyopia. Individual patients may be "cured" (no evidence of long-term glaucomatous progression) by effective surgery on the angle. The solid green line shows the effect of untreated glaucoma on an average population. The goal of treatment (represented by the dashed green line) is to delay the disease's onset (ie, shift the curve to the right) and decrease its severity (ie, reduce the progression to advanced visual impairment).

reduce the effects of specific environmental risks. Much work remains to be done before we can offer patients similar treatments for glaucoma.

WHAT NOW? WHAT NEXT?

Which risk alleles contribute to the common forms of glaucoma?

This question will be answered by appropriately designed, genome-wide studies of healthy controls and patients with glaucoma. Similar population-based studies helped researchers identify the *CFH Y402H* allele for age-related macular degeneration.[50-51] Individual groups are independently exploring the link between risk alleles and glaucoma, but no collaborative, multicenter, clinical studies are currently underway.

Do genetic modifiers affect the age of onset for various types of glaucoma?

At least two studies have identified a gene that influences the age at which people develop glaucoma. For example, patients with infantile glaucoma appear to have two mutated copies of *CYP1B1*, an autosomal recessive gene associated with a form of glaucoma that causes high IOP in infants.[52] The underlying mechanism of this genetic form of glaucoma is not presently known. A person who has one defective copy of *CYP1B1* may be more likely to develop juvenile- and adult-onset open-angle glaucoma at an earlier age than someone who does not have the mutated gene.[4]

Do genetic modifiers affect the severity of glaucoma?

The ability to determine if patients carry a specific genetic modifier would help clinicians identify the individuals who have the highest risk of developing glaucoma and who would benefit from earlier intervention. Conversely, careful monitoring would likely be appropriate for patients who did not have the marker.

Researchers have found that a mutated *tyr* gene is associated with the dysgenesis of ocular drainage structures in Cyp1b1-/-transgenic mice.[53] This finding in a mouse model is not directly applicable to humans because the same gene modifier has not been found in Saudi Arabian families who carry nonpenetrant *CYP1B1*.[54]

Do genetic markers influence the outcome of glaucoma treatments?

Our current approach to treating glaucoma is based on the disease's severity, the presence of comorbidities, the patient's compliance with therapy, the efficacy and adverse effects of drugs, and the cost of treatment. If medical therapy is appropriate, then we evaluate whether a patient is a "responder" or "nonresponder" and monitor him for adverse reactions after an initial trial of the chosen drug. It may be possible to streamline this process by performing pharmacogenomic association studies and using the results to test patients for genetic markers that affect their response to glaucoma medications.[55] The technology that could make this possible is the genotyping microarray, also known as a DNA chip.

In 2005, the FDA cleared a DNA microchip for genotyping certain cytochrome *P450* alleles known to alter the body's ability to metabolize drugs.[56] Altered drug metabolism directly affects therapeutic drug levels that correlate with efficacy and toxicity. For example, increased blood levels of absorbed timolol due to decreased metabolism can lead to cardiac side effects in susceptible individuals.[57]

Genetic markers may also affect the complex process of wound healing and thus the outcomes of glaucoma surgery.[58] It may be possible to test patients for alleles that raise their risk of delayed wound healing, increased scarring, or sensitivity to antifibrotic drugs. Markers associated with wound healing are unlikely to be found on the same genes as risk alleles for glaucoma.[59,60] The identification of markers that predict the outcomes of various treatments could, however, take the empiric guesswork out of determining the optimal glaucoma treatment for a given patient[59,60] and minimize the complications of glaucoma surgery.[61,62]

CONCLUSION

Quigley and Broman project that 60.5 million people worldwide will have glaucoma in 2010, and they estimate that the number of affected individuals will increase to 79.6 million by 2020.[30] They also extrapolate that the number of people with bilateral blindness from glaucoma will increase from 8.4 million in 2010 to 11.2 million in 2020.[30] These numbers necessitate improvements in clinicians' ability to diagnose glaucoma as well as the development of novel treatments to delay the disease's onset and decrease its severity (Figure 1).

Several caveats apply to the research efforts described herein. Genomic testing platforms must be (1) sensitive and accurate, (2) applicable to common forms of glaucoma across different subpopulations, (3) cost effective, and (4) able to provide valid predictive information about glaucoma's progression, its severity, and the outcomes of treatment.[28,63] If we researchers could develop a genomic diagnostic panel that met all of these requirements, we could use its results to develop personalized medical treatment for glaucoma. The large-scale implementation of such therapy might decrease the burden of glaucomatous visual impairment on public health. ❑

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1. Challa P. One view on the future of glaucoma genetics. *Glaucoma Today.* 2003;1(3).
2. Wiggs JL. Genetic etiologies of glaucoma. *Arch Ophthalmol.* 2007;125:30-37.
3. Wiggs JL, Allingham RR, Hossain A, et al. Genome-wide scan for adult onset primary open angle glaucoma. *Hum Mol Genet.* 2000;9:1109-1117.
4. Vincent AL, Billingsley G, Buys Y, et al. Digenic inheritance of early-onset glaucoma: CYP1B1, a potential modifier gene. *Am J Hum Genet.* 2002;70:448-460.
5. Nemesure B, Jiao X, He Q, et al. A genome-wide scan for primary open-angle glaucoma (POAG): the Barbados Family Study of Open-Angle Glaucoma. *Hum Genet.* 2003;112:600-609.
6. Inagaki Y, Mashima Y, Fuse N, et al. Polymorphism of beta-adrenergic receptors and susceptibility to open-angle glaucoma. *Mol Vision.* 2006;12:673-680.
7. Hashizume K, Mashima Y, Fumayama T, et al. Genetic polymorphisms in the angiotensin II receptor gene and their association with open-angle glaucoma in a Japanese population. *Invest Ophthalmol Vis Sci.* 2005;46:1993-2001.
8. Copin B, Brezin AP, Valtot F, et al. Apolipoprotein E-promoter single-nucleotide polymorphisms affect the phenotype of primary open-angle glaucoma and demonstrate interaction with the myocilin gene. *Am J Hum Genet.* 2002;70:1575-1581.
9. Iyengar SK. The quest for genes causing complex traits in ocular medicine: successes, interpretations, and challenges. *Arch Ophthalmol.* 2007;125:11-18.
10. Ridley M. *Nature Via Nurture: Gene, Experience, and What Makes Us Human.* New York: Harper Collins; 2003.
11. Drance S, Anderson DR, Schulzer M. Risk factors for progression of visual field abnormalities in normal-tension glaucoma. *Am J Ophthalmol.* 2001;131:699-708.
12. Gordon MO, Beiser JA, Brandt JD, et al. The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. *Arch Ophthalmol.* 2002;120:714-720; discussion 829-730.
13. Heijl A, Leske MC, Bengtsson B, et al. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. *Arch Ophthalmol.* 2002;120:1268-1279.
14. Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol.* 2002;120:701-713; discussion: 829-730.
15. Lichter PR, Musch DC, Gillespie BW, et al. Interim clinical outcomes in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medications or surgery. *Ophthalmology.* 2001;108:1943-1953.
16. Nouri-Mahdavi K, Hoffman D, Coleman AL, et al. Predictive factors for glaucomatous visual field progression in the Advanced Glaucoma Intervention Study. *Ophthalmology.* 2004;111:1627-1635.
17. Kalenak JW, Paydar F. Correlation of intraocular pressures in pairs of monozygotic and dizygotic twins. *Ophthalmology.* 1995;102:1559-1564.
18. Gottfredsdottir MS, Sverrisson T, Musch DC, Stefansson E. Chronic open-angle glaucoma and associated ophthalmic findings in monozygotic twins and their spouses in Iceland. *J Glaucoma.* 1999;8:134-139.
19. Thorleifsson G, Magnusson KP, Sulem P, et al. Common sequence variants in the LOXL1 gene confer susceptibility to exfoliation glaucoma. *Science.* 2007;317:1397-1400.
20. Klein BE, Klein R, Lee KE. Heritability of risk factors for primary open-angle glaucoma: the Beaver Dam Eye Study. *Invest Ophthalmol Vis Sci.* 2004;45:59-62.
21. Chang TC, Congdon NG, Wojciechowski R, et al. Determinants and heritability of intraocular pressure and cup-to-disc ratio in a defined older population. *Ophthalmology.* 2005;112:1186-1191.
22. van Koolwijk LM, Despriet DD, van Duijn CM, et al. Genetic contributions to glaucoma: heritability of intraocular pressure, retinal nerve fiber layer thickness, and optic disc morphology. *Invest Ophthalmol Vis Sci.* 2007;48:3669-3676.
23. Viswanathan AC, Hitchings RA, Indar A, et al. Commingling analysis of intraocular pressure and glaucoma in an older Australian population. *Ann Hum Genet.* 2004;68:489-497.
24. Charlesworth JC, Dyer TD, Stankovich JM, et al. Linkage to 10q22 for maximum intraocular pressure and 1p32 for maximum cup-to-disc ratio in an extended primary open-angle glaucoma pedigree. *Invest Ophthalmol Vis Sci.* 2005;46:3723-3729.
25. Duggal P, Klein AP, Lee KE, et al. Identification of novel genetic loci for intraocular pressure: a genomewide scan of the Beaver Dam Eye Study. *Arch Ophthalmol.* 2007;125:74-79.
26. Rotimi CN, Chen G, Adeyemo AA, et al. Genomewide scan and fine mapping of quantitative trait loci for intraocular pressure on 5q and 14q in West Africans. *Invest Ophthalmol Vis Sci.* 2006;47:3262-3267.
27. Radenbaugh PA, Goyal A, McLaren NC, et al. Concordance of aqueous humor flow in the morning and at night in normal humans. *Invest Ophthalmol Vis Sci.* 2006;47:4860-4864.
28. Collins CD, Purohit S, Podolsky RH, et al. The application of genomic and proteomic technologies in predictive, preventive, and personalized medicine. *Vascul Pharmacol.* 2006;45:258-267.
29. Hattenhauer MG, Johnson DH, Ing HH, et al. The probability of blindness from open-angle glaucoma. *Ophthalmology.* 1998;105:2099-2104.
30. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol.* 2006;90:262-267.
31. National Eye Institute Web site. Vision Problems in the US. Available at: http://www.nei.nih.gov/eyedata/tables.asp. Accessed December 7, 2007.
32. American Cancer Society Web site. Breast cancer facts & figures, 2005-2006. Available at: http://www.cancer.org/downloads/STT/CAFF2005BrF.pdf. Accessed December 7, 2007.
33. Bhisitkul RB. Vascular endothelial growth factor biology: clinical implications for ocular treatments. *Br J Ophthalmol.* 2006;90:1542-1547.
34. Bainbridge JW, Tan MH, Ali RR. Gene therapy progress and prospects: the eye. *Gene Ther.* 2006;13:1191-1197.
35. Sieving PA, Caruso RC, Tao W, et al. Ciliary neurotrophic factor (CNTF) for human retinal degeneration: phase I trial of CNTF delivered by encapsulated cell intraocular implants. *Proc Nat Acad Sci U.S.A.* 2006;103:3896-3901.
36. Haines JL, Hauser MA, Schmidt S, et al. Complement factor H variant increases the risk of age-related macular degeneration. *Science.* 2005;308:419-421.
37. Rivera A, Fisher SA, Fritsche LG, et al. Hypothetical LOC387715 is a second major susceptibility gene for age-related macular degeneration, contributing independently of complement factor H to disease risk. *Hum Mol Genet.* 2005;14:3227-3236.
38. Gold B, Merriam JE, Zernant J, et al. Variation in factor B (BF) and complement component 2 (C2) genes is associated with age-related macular degeneration. *Nat Genet.* 2006;38:458-462.
39. Yang Z, Camp NJ, Sun H, et al. A variant of the HTRA1 gene increases susceptibility to age-related macular degeneration. *Science.* 2006;314:992-993.
40. SanGiovanni JP, Chew EY, Clemons TE, et al. The relationship of dietary carotenoid and vitamin A, E, and C intake with age-related macular degeneration in a case-control study: AREDS Report No. 22. *Arch Ophthalmol.* 2007;125:1225-1232.
41. Seddon JM. Multivitamin-multimineral supplements and eye disease: age-related macular degeneration and cataract. *Am J Clin Nutr.* 2007;85:304S-307S.
42. Smith W, Assink J, Klein R, et al. Risk factors for age-related macular degeneration: Pooled findings from three continents. *Ophthalmology.* 2001;108:697-704.
43. Francis PJ, George S, Schultz DW, et al. The LOC387715 gene, smoking, body mass index, environmental associations with advanced age-related macular degeneration. *Hum Hered.* 2007;63:212-218.
44. Biglan AW, Hiles DA. The visual results following infantile glaucoma surgery. *J Pediatr Ophthalmol Strabismus.* 1979;16:377-381.
45. Mandal AK, Gothwal VK, Bagga H, et al. Outcome of surgery on infants younger than 1 month with congenital glaucoma. *Ophthalmology.* 2003;110:1909-1915.
46. Mendicino ME, Lynch MG, Drack A, et al. Long-term surgical and visual outcomes in primary congenital glaucoma: 360 degrees trabeculotomy versus goniotomy. *J AAPOS.* 2000;4:205-210.
47. Gramer E, Tausch M, Kraemer C. Time of diagnosis, reoperations and long-term results of goniotomy in the treatment of primary congenital glaucoma: a clinical study. *Int Ophthalmol.* 1996;20:117-123.
48. Morgan KS, Black B, Ellis FD, Helveston EM. Treatment of congenital glaucoma. *Am J Ophthalmol.* 1981;92:799-803.
49. Cai Y, Li MY, Shen YY, Liu LN. Long-term effect of trabeculotomy on primary congenital glaucoma [in Chinese]. *Zhonghua Yan Ke Za Zhi.* 2004;40:733-736.
50. Klein RJ, Zeiss C, Chew EY, et al. Complement factor H polymorphism in age-related macular degeneration. *Science.* 2005;308:385-389.
51. Edwards AO, Ritter R III, Abel KJ, et al. Complement factor H polymorphism and age-related macular degeneration. *Science.* 2005;308:421-424.
52. Stoilov I, Akarsu AN, Sarfarazi M. Identification of three different truncating mutations in cytochrome P4501B1 (CYP1B1) as the principal cause of primary congenital glaucoma (buphthalmos) in families linked to the GLC3A locus on chromosome 2p21. *Hum Mol Genet.* 1997;6:641-647.
53. Libby RT, Smith RS, Savinova OV, et al. Modification of ocular defects in mouse developmental glaucoma models by tyrosinase. *Science.* 2003;299:1578-1581.
54. Bidinost C, Hernandez N, Edward DP, et al. Of mice and men: tyrosinase modification of congenital glaucoma in mice but not in humans. *Invest Ophthalmol Vis Sci.* 2006;47:1486-1490.
55. Shastry BS. Pharmacogenetics and the concept of individualized medicine. *Pharmacogenomics J.* 2006;6:16-21.
56. Abramowicz ME. AmpliChip CYP450 test. *Med Lett Drugs Ther.* 2005;47:71-72.
57. Edeki TI, He H, Wood AJ. Pharmacogenetic explanation for excessive beta-blockade following timolol eye drops. Potential for oral-ophthalmic drug interaction. *JAMA.* 1995;274:1611-1613.
58. Bruno C, Fisher G, Moroi S. Is "scarless wound healing" applicable to glaucoma surgery? *Expert Rev Ophthalmol.* 2007;2:79-90.
59. McLaren N, Reed DM, Musch DC, et al. Evaluation of the beta2-adrenergic receptor gene as a candidate glaucoma gene in 2 ancestral populations. *Arch Ophthalmol.* 2007;125:105-111.
60. McLaren NC, Moroi, S.E. Clinical implications of pharmacogenetics for glaucoma therapeutics. *Pharmacogenomics J.* 2003;3:197-201.
61. Halkiadakis I, Lim P, Moroi SE. Surgical results of bleb revision with scleral patch graft for late-onset bleb complications. *Ophthalmic Surg Lasers Imaging.* 2005;36:14-23.
62. Oyakhire JO, Moroi SE. Clinical and anatomical reversal of long-term hypotony maculopathy. *Am J Ophthalmol.* 2004;137:953-955.
63. Despriet DD, Klaver CC, van Duijn CC, Janssens AC. Predictive value of multiple genetic testing for age-related macular degeneration. *Arch Ophthalmol.* 2007;125:1270-1271.