

## Abstracts of Asian research published in the international literature

### Trabeculectomy with Beta Radiation: Long-term Follow-up

In a retrospective non-comparative case series, the long-term outcome and complications of trabeculectomy with beta radiation were evaluated. Patients with confirmed primary open angle glaucoma (POAG), who received trabeculectomy with adjunctive beta radiation at the Prince of Wales Hospital, Hong Kong, between June 1991 and November 1994 were evaluated. Patients fulfilling the preceding criteria were followed up longitudinally. The visual acuity, intraocular pressure (IOP), bleb morphology, and complications were evaluated. Main outcome measures included visual acuity, IOP, bleb morphology, and complications.

Forty three eyes of 43 consecutive Chinese patients were recruited and successfully followed up for a minimum of 7 years. The mean age  $\pm$  1 standard deviation (SD) was  $60.9 \pm 13.0$  years. There were 29 men and 14 women. The mean baseline IOP  $\pm$  1 SD was  $28.3 \pm 5.8$  mm Hg. The mean postoperative IOP  $\pm$  1 SD after the initial trabeculectomy was  $11.9 \pm 4.3$  mm Hg, and the mean number of preoperative IOP-lowering eyedrops  $\pm$  1 SD was reduced from  $2.8 \pm 0.5$  to  $0.7 \pm 1.0$  at 7 years follow up. The qualified success rate at 7 years follow up, defined as IOP  $\leq 21$  mm Hg with/without medication(s), was 88.4%. The complete success rate at 7 years defined as IOP  $\leq 21$  mm Hg without medication was 60.7%. Two eyes developed blebitis, and one progressed to corneal decompensation after the infection. One eye had hypotony, and one eye had a traumatic ruptured bleb. Twelve eyes (27.9%) developed significant cataract. No corneal ulceration or scleral necrosis was encountered.

Trabeculectomy with a single dose of 1000 rad beta radiation used as an adjunctive measure for POAG in Chinese eyes achieved a qualified success rate of 88.4% at 7 years.

Lai JS, Poon AS, Tham CC, Lam DS. Trabeculectomy with beta radiation: long-term follow-up. *Ophthalmology* 2003;110:1822-1826.

### Interventions for Angle Closure Glaucoma

Primary angle closure is one of the leading causes of blindness in East Asia. At present, there are few clinical guidelines on the optimal treatment of acute angle closure (AAC) or primary angle closure (PAC) in the affected or contralateral eye. This study was performed to assess the interventions for treating AAC and PAC with or without glaucomatous optic neuropathy.

All randomised clinical trials, prospective controlled clinical trials, non-prospective controlled clinical trials, and retrospective case series with  $>50$  patients that evaluated treatments for AAC or PAC were included. Studies published in the English language were identified from Medline, PubMed, EMBASE, and the Cochrane Collaboration, as well as by a hand search of the reference lists of important articles.

Nine randomised clinical trials and 24 non-randomised clinical trials and large case series were evaluated. Laser peripheral iridotomy (LPI) has been found to be as effective as surgical peripheral iridectomy in randomised clinical trials of the affected and contralateral eyes of patients with AAC or PAC with or without evidence of glaucoma. In another randomised clinical trial, latanoprost was found to decrease

intraocular pressure (IOP) more than timolol for PAC in patients for whom LPI alone failed.

This review suggests that LPI should be recommended for the treatment of affected and contralateral eyes of AAC patients. In patients with PAC and insufficient treatment with LPI, latanoprost eye drops may decrease IOP more than timolol. There is still insufficient evidence about other interventions for the treatment of AAC and PAC.

Saw SM, Gazzard G, Friedman DS. Interventions for angle-closure glaucoma: an evidence-based update. *Ophthalmology* 2003;110:1869-1878.

### Association of Intraocular Pressure with Glaucomatous Optic Neuropathy

This study was performed to examine the relationship between intraocular pressure (IOP), anthropomorphic, demographic, socioeconomic, systemic, and ocular factors and glaucomatous optic neuropathy (GON) in Chinese people. 2000 Chinese people aged 40 to 79 years were selected from the Singapore electoral register. Of the 1717 people considered eligible for examination, 1232 participated, representing a response rate of 71.8%. IOP was estimated with Goldmann applanation tonometry. The drainage angle was assessed with static and dynamic gonioscopy. The optic nerve was examined at high magnification through a dilated pupil with a fundus contact lens or a +78 D lens. Static automated visual field testing was performed on subjects with suspected glaucoma. GON was diagnosed on the basis of structural and functional abnormalities of the optic nerve.

The main independent determinants of higher IOP were higher systolic blood pressure ( $p < 0.001$ ), quadrants of any peripheral anterior synechiae (PAS,  $p = 0.02$ ),



and width of the drainage angle ( $p = 0.049$ ). A 100  $\mu\text{m}$  increase in corneal thickness was associated with an increase in mean IOP of 1.5 to 1.8 mm Hg ( $p < 0.001$ ). Odds of GON increased 1.2 times per 1 mm Hg increase in screening IOP. A clear association between corneal thickness and GON was not identified.

Clinical IOP estimates are related to systolic blood pressure and corneal thickness. Variation in IOP with angle width may suggest that trabecular compaction significantly contributes to increases in IOP, independent of angle closure. GON is an IOP-related phenomenon among Chinese Singaporeans.



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Foster PJ, Machin D, Wong TY, et al. Determinants of intraocular pressure and its association with glaucomatous optic neuropathy in Chinese Singaporeans: the Tanjong Pagar Study. *Invest Ophthalmol Vis Sci* 2003;44:3885-3891.

## **R368H Causing Primary Congenital Glaucoma**

This study investigated the predominant mutation in the CYP1B1 gene in patients in India with primary congenital glaucoma (PCG), using polymerase chain reaction (PCR)-restriction fragment length polymorphism (RFLP) methods and characterised the molecular defect in 2 generations of an affected family. DNA samples from 146 patients with PCG from 138 pedigrees were analysed for several distinct mutations in CYP1B1 by PCR-RFLP.

PCR-RFLP screening revealed that 30.8% of patients were positive for any one of the 6 mutations (376insA, 528G→A, 923C→T, 959G→A, 1449G→A, and 1514C→A), and 17.8% of the patients were found to have the rarely reported mutation R368H (1449G→A). All mutations were confirmed by DNA sequencing.

These results suggest extensive allelic heterogeneity in Indian patients with PCG, with the predominant allele being R368H

among the 146 Indian patients tested. It appears possible to use this approach for carrier detection in pedigrees with a positive family history and in population screening. The approach also offers a method for rapid screening of potential carriers and affected individuals.

Reddy AB, Panicker SG, Mandal AK, et al. Identification of R368H as a predominant CYP1B1 allele causing primary congenital glaucoma in Indian patients. *Invest Ophthalmol Vis Sci* 2003;44:4200-4203.

## **Optineurin Mutation Pattern in Primary Open Angle Glaucoma**

The optineurin (OPTN) gene is the second gene besides MYOC in which mutations have been identified to be associated with primary open angle glaucoma (POAG). In this study, sequence alterations in the OPTN gene associated with POAG in Chinese people were investigated. All the coding exons of OPTN were screened for sequence alterations, including the intron-exon boundaries, by polymerase chain reaction-conformation-sensitive gel electrophoresis and DNA sequencing in a group of 119 Chinese patients with POAG and 126 unrelated controls.

Sixteen sequence changes were identified: 3 had been reported (T34T, M98K, and R545Q) and 13 were novel (T49T, E103D, V148V, P199P, T202T, H486R, IVS6-5T→C, IVS6-10G→A, IVS7+24G→A, IVS8+20G→A, IVS13+21C→G, IVS15+10G→A, and IVS15-48C→A). Among these changes, only E103D, H486R, V148V, and IVS13+21C→G were found exclusively in patients with POAG, whereas P199P, T202T, and IVS8+20G→A were present only in the controls. The genotype of IVS7+24G→A showed a significant association with POAG ( $p = 0.02$ , Fisher two-tailed exact test) and with increased cup-to-disc ratio in these patients ( $p = 0.005$ , Mann-Whitney test).

The findings of this study enrich the evidence of the OPTN gene as a causative

gene for POAG and suggest a different mutation pattern of OPTN in Chinese people than in Caucasians. The wide spectrum of putative mutations detected in this study suggests that both structural and functional disruptions in OPTN may contribute to the pathogenesis of glaucoma.

Leung YF, Fan BJ, Lam DS, et al. Different optineurin mutation pattern in primary open-angle glaucoma. *Invest Ophthalmol Vis Sci* 2003;44:3880-3884.

## **Risk Factors for Cataracts in a Chinese Population**

This study was performed to describe risk factors for nuclear, cortical, and posterior subcapsular (PSC) cataracts in Chinese Singaporeans. A population-based cross sectional study involved ethnic Chinese men and women aged 40 to 81 years. A stratified, clustered, disproportionate (more weights to older people), random sampling procedure was used to initially select 2000 Chinese names of people aged 40 to 79 years from the 1996 electoral register in the Tanjong Pagar district in Singapore. Eligible people ( $n = 1717$ ) were invited for a standardised ocular examination and interview at a centralised clinic, following which an abbreviated examination was conducted for non-respondents in their homes. Cataract was graded clinically using the lens opacity classification system (LOCS) III. The main outcome measures were adjusted odds ratio for risk factors for specific cataract types (nuclear, cortical and PSC), any cataract, and cataract surgery, examined in multiple logistic regression models.

Of the 1232 people (71.8%) examined, 1206 (70.2%) provided lens data for this analysis. Increasing age was associated with all cataract types, any cataract, and cataract surgery. There was no significant sex difference in the presence of any

cataract, specific cataract types or cataract surgery. After controlling for age, sex, and other factors, diabetes was associated with cortical cataract (3.1; 95% confidence interval [CI], 1.6-6.1), PSC cataract (2.2; 95% CI, 1.2-4.1), any cataract (2.0; 95% CI, 0.9-4.5), and cataract surgery (2.3; 95% CI, 1.3-4.1). Lower body mass index was associated with cortical cataract (1.8; 95% CI, 1.1-2.9; lowest versus highest quintile) and any cataract (2.3; 95% CI, 1.3-4.0). Current cigarette smoking was associated with nuclear cataract (1.7, 95% CI, 1.0-2.9; more than 10 cigarettes per day versus none).

A non-professional occupation was associated with nuclear cataract (2.9; 95% CI, 1.5-5.8; for production or machine operators and 2.6; 95% CI, 1.2-5.5; for labourers or agricultural workers, both versus professionals). Lower education was associated with nuclear cataract (2.3; 95% CI, 1.0-5.2, none versus tertiary), while lower household income was associated with PSC cataract (4.7, 95% CI, 1.1-20.0; income <S\$2000 versus >S\$4000).

Age-related cataracts are associated with a variety of risk factors among Chinese people in Singapore, similar to those reported in European, Indian, and African populations. These data support common aetiological mechanisms for age-related cataracts, irrespective of ethnic origin.

Foster PJ, Wong TY, Machin D, et al. Risk factors for nuclear, cortical and posterior subcapsular cataracts in the Chinese population of Singapore: the Tanjong Pagar Survey. *Br J Ophthalmol*. 2003;87: 1112-1120.

### **Myocilin Mutations in Patients with Primary Open Angle Glaucoma**



This study was performed to screen for mutations in the MYOC gene of patients with primary open angle glaucoma (POAG) in India and to better understand the mutations using a possible model of myocilin. DNA was analysed for mutations in 107 patients with POAG and 90 controls. The exonic sequences of the MYOC gene from all subjects were amplified by polymerase chain reaction (PCR). Single strand conformation polymorphism (SSCP) was performed for all the PCR products. The DNA samples that showed mobility shift in the banding pattern in SSCP gel were sequenced. The presence of the common mutation Gln368Stop was analysed using a specific restriction enzyme Taa 1. The mutations observed here and elsewhere have been mapped onto a possible model built for myocilin using a knowledge-based consensus modelling approach.

Two heterozygous mutations, Gly367Arg (1099G>A) and Thr377Met (1130C>T), were identified in exon3 of the MYOC gene of probands 40-1 and 51-1, respectively, from material obtained from the 107 unrelated patients with POAG. These two mutations were not present in the controls. A single nucleotide polymorphism (SNP), Gly122Gly (366C>T), was identified in exon1 of proband 57-1 as a non-disease causing variation. The common mutation, Gln368Stop, found in Western populations was not observed in the Indian patients with POAG screened in this study.

The possible structural model for myocilin suggests a predominantly  $\beta$ -strand rich C-terminal region (181-504), which is connected by the  $\alpha$ -helical mid-region (111-180) to the N-terminal region (34-110), which has low secondary structure content. Both the mutations, Gly367Arg and Thr377Met, identified in this study map on to the C-terminal region. These mutations disfavour burial of this region during oligomer formation due to the charged or bulky nature of the mutants. Most of the other mutations known for myocilin are also surface exposed on the C-terminal region.

These findings indicate that the mutation frequency of the MYOC gene is 2% in the Indian population affected with POAG, which is not a well-studied ethnic group on the Asian continent. The variations identified in this study have been previously reported in Western populations. The non-sense mutation, Gln368Stop, was not observed in the present study, suggesting that it may not be a common disease-causing mutation in the Indian population. Amongst other Asian populations, studies from Japan also did not report this non-sense mutation. The location of these mutations suggest that a plausible mode of action could be by disruption of dimer or oligomer formation by the C-terminal region allowing greater chances of nucleation of aggregation by the N-terminal region.

Kanagavalli J, Krishnadas SR, Pandaranayaka E, et al. Evaluation and understanding of myocilin mutations in Indian primary open angle glaucoma patients. *Mol Vis* 2003;9:606-614.

