Age-related Macular Degeneration in Asia

BY WAI-MAN CHAN, FRCP, FRCOPHTH

Age-related macular degeneration (AMD) is a major cause of blindness in the elderly in Asian countries, and the number is growing significantly. This may be due to the urbanization of Asian populations, Westernization of lifestyles, and increasing disease awareness. Much of our past understanding of AMD comes from studies in white and black populations. With more information exchange and recent publications from Asia, however, we know that AMD in Asia has its own perspective in terms of epidemiology, genetics, phenotypic presentation, clinical subtype, and management.

Epidemiology of AMD in Asia

Asia has mixed populations of different races and ethnicities. Studies on prevalence of AMD in Asia show wide variation in results, some of them even conflicting. The perception that AMD is much less common in Asians than in whites may no longer be true with increasing evidence from recent population-based studies. The Hisayama Study in Japan reported that, in a Japanese population aged 50 years of age or older, the prevalence of early AMD was 12.7% and late AMD was 0.87%. The frequency of neovascular AMD was significantly higher in the men. The Singapore Malay Eye Study demonstrated the prevalence of early AMD and late AMD in Singapore Malay aged 40 to 80 years to be 3.5% and 0.34%, respectively. The Shihpai Eye Study in Taiwan studied an elderly Chinese population 65 years of age or older and showed the prevalence of early AMD was 9.2% and of late AMD was 1.9%. In the Beijing Eye Study in China, the prevalence of early and late AMD in Chinese persons 40 years and older was reported to be low as 1.4% and 0.2%, respectively. The overall impression was that the prevalence of AMD in Asians is not greatly different from that in whites (Table 1). Other than race, the proportion of dense cataract that made fundus pictures ungradable, different levels of industrialization, dietary intakes, and other environmental factors might account for the disparity in prevalence among Asian populations.

Two diseases that are commonly found in Asians can also affect the accuracy in diagnosis of AMD. One is central serous chorioretinopathy, which presents with pigmentary changes at the posterior pole with or without associated scattered drusen, and it may masquerade as early AMD. Another is polypoidal choroidal vasculopathy (PCV), which can manifest similarly as late AMD. Future research in Asia will begin to evaluate incidence and risk factors.

Genetics of AMD in Asia

Genetic susceptibility also plays a role in the development of AMD. There are differences in the occurrence of disease-susceptible genes and single nucleotide polymorphisms (SNPs) between white and Asian populations. The complement factor H (CFH) gene is involved in chronic inflammatory response and drusen formation, and it was the first strong genetic factor identified for exudative AMD. The Y402H is present in 34.9% of Caucasian populations, and was estimated to play a role in almost 60% of AMD at the population level. The frequencies are low in Chinese and Japanese, and no obvious associations with wet AMD were found in these two populations (Table 2). In contrast, the CFH polymorphism Tyr402His

<table>
<thead>
<tr>
<th>Population</th>
<th>Japanese</th>
<th>Chinese</th>
<th>Chinese</th>
<th>Malay</th>
<th>Indian</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study (region)</td>
<td>The Hisayama Study (Japan)</td>
<td>The Beijing Eye Study (China)</td>
<td>The Shihpai Eye Study (Taiwan)</td>
<td>The Singapore Malay Eye Study (Singapore)</td>
<td>Andhra Pradesh Eye Study (India)</td>
</tr>
<tr>
<td>Early AMD</td>
<td>12.70%</td>
<td>1.40%</td>
<td>9.20%</td>
<td>3.50%</td>
<td>--</td>
</tr>
<tr>
<td>Late AMD</td>
<td>0.90%</td>
<td>0.20%</td>
<td>1.90%</td>
<td>0.30%</td>
<td>1.90%</td>
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</table>
appears to be strongly linked to the pathogenesis of AMD in the Indian population.\textsuperscript{11}

Other genetic factors, such as HTRA1 serine protease gene (SNP rs11200638) and hypothetical LOC387715 (SNP rs10490924), were detected in Chinese\textsuperscript{12} and white\textsuperscript{13} patients with late AMD at a similar frequency, showing strong association with CNV formation. The two major genes, CFH and HTRA1, are hypothesized to govern two different biological mechanisms: CFH affects drusen formation in dry AMD, and HTRA1 influences CNV, the hallmark of wet AMD. This may account the distinct AMD phenotypes between Asian and white populations, and the mixed phenotypes in certain cases because of gene-gene and gene-environment interactions.\textsuperscript{14-16}

### Clinical Subtype of AMD in Asian Populations

Exudative AMD is classified as classic and occult CNV by fluorescein angiography. Recently, with the expanding use of indocyanine green angiography (ICGA) to delineate choriocapillaris abnormality, new clinical entities such as PCV and retinal angiomatous proliferation (RAP) have emerged. Each clinical entity is characterized by differences in clinical course, phenotypic presentation, pathogenesis, and outcomes with treatment (Table 3). In a study of 155 patients with exudative AMD in a Chinese population, 68% had CNV of typical AMD, 25% had PCV, 5% had RAP, and 3% had mixed lesions.\textsuperscript{17} In another series of 158 Japanese patients with exudative AMD, 55% were diagnosed as PCV, 35% as typical AMD and 5% as RAP and 5% had mixed lesions.\textsuperscript{18}

ICGA is the gold standard for the definitive diagnosis and characterization of PCV (Figure 1). Highly suspicious signs of PCV rendering ICGA highly recommended are massive subretinal hemorrhage, hemorrhagic pigment epithelial detachments, notched pigment epithelial detachments, absence of soft drusen, clinically visible orange-red subretinal nodules, and presentation in middle-aged patient.

### Treatment for Exudative AMD in Asian Populations

For typical neovascular AMD, intravitreal anti-vascular endothelial growth factor (VEGF) monotherapy is

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### Table 2. Associations, Genotypes, Frequencies, and Odds Ratios of Susceptible Genes and SNPs

<table>
<thead>
<tr>
<th>Gene</th>
<th>Single nucleotide polymorphisms (SNPs)</th>
<th>Chinese\textsuperscript{8,9,12,16}</th>
<th>Japanese\textsuperscript{10,14}</th>
<th>Indian\textsuperscript{11,15}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complement factor H (CFH)</td>
<td>Y402H polymorphism rs1061170;T&gt;C</td>
<td>No association</td>
<td>No association</td>
<td>Strong association</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>52% in cases and 26% in controls; odds ratio 11.52 for the CC genotype</td>
</tr>
<tr>
<td>Other SNPs of CFH</td>
<td>Slightly increased the susceptibility</td>
<td>Slightly increased the likelihood</td>
<td></td>
<td>Significantly increased the risk</td>
</tr>
<tr>
<td>Promoter of high-temperature requirement A-1 (HTRA1) genes on chromosome 10q26</td>
<td>rs11200638;G&gt;A</td>
<td>Strong association</td>
<td>Strong association</td>
<td>Strong association</td>
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<td></td>
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<td>odds ratio was 10.00 for the AA genotype (Hong Kong Chinese); 67.8% in cases vs 42.4% in controls; odds ratio was 7.90 for the AA genotype (Beijing Chinese)</td>
<td>odds ratio was 69% in cases vs 32% in controls; odds ratio was 10.02 for the AA genotype</td>
<td>68.7% in cases vs 34.5% in controls; odds ratio was 6.69 for the AA genotype</td>
</tr>
<tr>
<td>Hypothetical LOC387715 in the chromosome 10q26 region (upstream of HTRA1)</td>
<td>rs10490924;G&gt;T</td>
<td>Strong association</td>
<td>Strong association</td>
<td>Strong association</td>
</tr>
<tr>
<td></td>
<td></td>
<td>odds ratio was 11.14 for the AA genotype (Hong Kong Chinese); 64.9% in cases vs 43.2% in controls; odds ratio was 5.45 for the TT genotype (Beijing Chinese)</td>
<td>odds ratio was 68% in cases vs 33% in controls; odds ratio was 6.20 for the TT genotype</td>
<td>61.9% in cases vs 35.8% in controls; odds ratio was 8.24 for the TT genotype</td>
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still the preferred primary treatment if it is available. The choice between ranibizumab (Lucentis, Genentech, Inc.) and bevacizumab (Avastin, Genentech, Inc.) in Asia depends mostly on accessibility of the treatment in the medical system, affordability for the patient, and physician preference.\textsuperscript{19,20} The most favorable option suggests that three monthly intravitreal doses of either anti-VEGF agent are administered to maximize the initial response to treatment, followed by an individualized maintenance phase during which patients should receive treatment based on their individual response according to the visual outcomes and optical coherence tomography (OCT) findings. From the experiences of treatment with...
ranibizumab and bevacizumab in Asian populations, there were no apparent differences in visual acuity outcomes, injection rates, or safety profiles between East and West. Combination therapy with anti-VEGF and photodynamic therapy (PDT) may be considered for those with persistent disease despite anti-VEGF monotherapy or with the intention to reduce the number of retreatments.

For the clinical subtype with PCV, PDT has been well accepted to be an effective treatment modality. PDT has shown good results for PCV, with stable or improved vision at 1-year follow-up, achieved in 81% to 100% of patients. However, extensive subretinal hemorrhages are an unavoidable side effect of PDT in some eyes with PCV—and PDT becomes less effective in PCV with late presentation and cases with secondary growth of fibrovascular tissue. Anti-VEGF monotherapy has been studied in PCV and demonstrated to improve visual acuity and outcomes measured by OCT, but it results in only minimal or no regression of polyps as measured by ICGA. It may be hypothesized that in PCV, combining PDT’s angiocclusive effect on polyps with anti-VEGF’s antipermeability effect on exudative changes associated with PCV may lead to better clinical outcomes (Figure 2). Further studies are needed to determine the role of combination therapy as primary therapy for treating PCV.

CONCLUSIONS
The magnitude and awareness of AMD in Asia are growing. AMD in Asian populations have many differences from the Western populations, especially in phenotype manifestations and prevalence of clinical subtypes. Diversity in genetic composition and environmental interactions are among the reasons. Accurate diagnoses of AMD subtypes are important for appropriate patient management. PCV constitutes a high percentage of patients with exudative AMD in Asian populations, and it is known that anti-VEGF therapy alone may result in suboptimal anatomic and angiographic results. Once the diagnosis of PCV is made by

Figure 2. A 59-year-old woman presented with serosanguinous maculopathy in her right eye secondary to an active polypoidal choroidal vasculopathy. The presenting color photography (A), fluorescein angiography (B) and ICGA (C) are in the upper panel, and the baseline BCVA was 20/200. Photodynamic therapy and intravitreal anti-VEGF with bevacizumab were delivered. The BCVA improved to 20/30 at 1-year follow-up. The hard exudates and hemorrhage resolved gradually and completely disappeared 12 months after treatment (D). There was no angiographic leakage and the hemorrhagic pigment epithelium detachment had resolved (E). ICGA also demonstrated regression of the polyps and interconnecting vessels (F).
ICGA, modifications in therapeutic protocol, by including PDT, may be indicated in order to improve the outcomes for this disease subgroup.

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