Age related maculopathy

Timely translation of ophthalmic research into clinical practice

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Collaboration is the key

The goal of all of the major federal funding agencies for medical research is to shorten the time between basic research discoveries and implementation at the "bedside" to improve human health. To that end, the National Institutes of Health in the United States (<http://nihroadmap.nih.gov/clinicalresearch/overview-translational.asp>), the Medical Research Council in the United Kingdom (www.mrc.ac.uk), and the Canadian Institutes of Health Research (<http://www.cihr-irsc.gc.ca/cgi-bin/print-imprimer.pl>) have all instituted strategies aimed at translating research for the public good. At the core of all these strategies is the need for interdisciplinary, collaborative research involving both clinicians and scientists. What does this mean for ophthalmology and how can ophthalmologists and vision researchers contribute to this global effort to translate research results to improve patient care? The current status of research into the aetiology and treatment of age related macular degeneration (AMD), the leading cause of blindness in the elderly in developed countries, provides a topical example.

The paper by Xu *et al*¹ in this month's issue of the *BJO* (p 1087) represents a landmark: the first English language report of risk factors for AMD in a Chinese population. A PubMed literature search using the search strategy "AMD AND risk factor AND China" conducted in June 2006 revealed only four papers, three of them published in Chinese, with the most recent published in 1992.

Of the four previously published papers on AMD risk factors in China, the one English language paper was published in 2000, the authors concluding from their data that apolipoprotein E4 (apoE4) is unlikely to be an important risk factor for AMD in Chinese in part because of the lower allele frequency in comparison with white people.² Interestingly, the association between apoE4 and AMD that was observed in the Chinese cohort, although not statistically significant owing to a relatively small sample size, is similar to what has been observed in

white populations.³ A paper by Ioannidis *et al* supports the conclusion that the biological impact of genetic markers, such as apoE, is usually consistent across populations, although the frequency of the markers themselves varies by sex/ethnicity.⁴ It is important to have data from various populations to allow comparison of results and to provide clues about disease aetiology.

Complement factor H gene, involved in immunity, was recently estimated to explain up to 74% of AMD.⁵ Unfortunately, the published data related to complement factor H and AMD have only been quantified in white people and there are no data on population based allele frequencies in other ethnic groups. How does the epidemiologic data support the genetic results? A recent review of the epidemiology of AMD does not list biological markers of infection or inflammation,⁶ presumably because, unlike the genetic data, the epidemiological data have been inconsistent.

Future research into the aetiology of AMD (and other ocular conditions) needs to include both genetic and environmental risk factors

Although clearly important, genetics is not the sole determinant of AMD prevalence and incidence in the population. A twin study by Seddon *et al*⁷ found that genetic factors explain 46% to 71% of the variation in disease severity while environment explains 19% to 42%. Twenty seven per cent of AMD is estimated to be the result of smoking in New Zealand⁸ and 28 000 cases of AMD in people aged 75+ in the United Kingdom may be caused by smoking.⁹ A surprising finding in the Beijing Eye Study was the lack of an association between cigarette smoking and AMD prevalence where most previous studies have not only found a positive association, but also demonstrated dose-response, temporality, and reversibility of effect.¹⁰ A gene-environment interaction has been found for apoE and cigarette smoking,¹¹ as well as the

complement factor H gene and cigarette smoking.¹² Perhaps the lack of an association between cigarette smoking and AMD prevalence in the Beijing Eye Study is caused by an unmeasured gene-environment interaction.

So what do these previous research results mean for future research and current clinical practice? To date, there has been little information to support primary prevention strategies. In Australia, data about the attributable risk of AMD and blindness due to cigarette smoking, estimated at between 14% and 20% in Australia, have been used in public health campaigns to decrease smoking rates (<http://www.quitnow.info.au/damage/eyeexp.htm>). In terms of secondary prevention, the recent genetic discoveries could lead to molecular targets for drug development and ultimately pharmacogenetics may assist physicians in personalised prescribing for patients but this may take many years. Until new therapies are available, one area of research that could immediately benefit patient care is the development of algorithms for risk prediction. For example, it would be useful for a physician to be able to tell a patient what their lifetime risk of developing AMD is if they have a family history of AMD and are a smoker compared to a non-smoker with no family history of AMD. These risk strata can be developed for all identified risk factors. Until reliable genetic tests are available and appropriate for clinical use, family history could serve as a proxy for genetic markers. To develop risk prediction models that have clinical utility, relevant data need to be collected in various racial/ethnic groups. Future research into the aetiology of AMD (and other ocular conditions) needs to include both genetic and environmental risk factors. This will allow the promise of personalised medicine to be reached in the field of ophthalmology.

In conclusion, continued collection of environmental and genetic data related to AMD and other ocular conditions of public health importance is needed for various racial/ethnic groups. Clinicians and scientists should work together to define clinically relevant research questions and then to answer them, such that the results can be used to enhance clinical practice and improve patient care. This is especially important in this era of decreasing funding for research. With the ageing of the population, AMD and other age related ocular conditions and associated blindness will increase unless true multidisciplinary, collaborative research is undertaken to shorten the time between scientific discovery and clinical application.

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Foveal hypoplasia

Chicken and egg

J Sloper

Implications for our understanding of the mechanisms of early development of the visual pathway

Our high resolution, three dimensional view of the world depends on the presence of foveas to give high acuity, on an optic chiasm to direct information from the corresponding areas of nasal and temporal retina to the same hemisphere and on the alignment of the visual axes to allow corresponding features in the image from each eye to be aligned and combined into a single stereoscopic percept. Coordinating the development of these different components into an integrated binocular visual system poses a considerable challenge and it is not surprising that defects arise from time to time.

The most common genetic condition to affect chiasmal development is albinism, in which the fovea is hypoplastic and the fundus is hypopigmented. There is misrouting of retinal ganglion cell axons at the optic chiasm and binocular function is reduced or absent. It has generally been assumed that the foveal hypoplasia and excessive crossing of retinal axons at the optic chiasm resulted from deficient synthesis of melanin, although the mechanisms involved have not been determined.¹ In this issue of *BJO* (p 1098) van Genderen *et al*² describe three patients with foveal hypoplasia and electrophysiological findings typical of the chiasmal misrouting found in albinism, but with normal fundal pigmentation. Two were sisters who had been considered to have

congenital idiopathic oculomotor nystagmus, while the third had been diagnosed with Kartagener syndrome (primary ciliary dysgenesis and situs inversus) with nystagmus. The observation that foveal hypoplasia and chiasmal misrouting can occur in the presence of normal pigmentation is of considerable interest.

Firstly, these findings confirm that foveal hypoplasia can occur in the absence of hypopigmentation. This has also been described in aniridia,³ but those patients did not show electrophysiological evidence of chiasmal misrouting, demonstrating that normal chiasmal development can occur in the presence of foveal hypoplasia. Van Genderen *et al* suggest that rather than foveal hypoplasia causing chiasmal misrouting, as is generally thought, the relation may be the other way round, with chiasmal misrouting interfering with foveal development. This has substantial implications for our understanding of the mechanisms of early development of the visual pathway. It would imply, for example, that the primary defect in their patients, and also in albinism, is in axonal misrouting at the optic chiasm, with the foveal hypoplasia being secondary to this. In contrast, in aniridia the failure would be in a retrograde signalling mechanism from ganglion cell axons and their central targets to the retina in the presence of a normal chiasm. It is

interesting in this respect that the pattern of abnormality of retinal vasculature is different in albinism and aniridia.³ Retinal blood vessels are excluded from the foveal region during normal development⁴ so this difference in vasculature could indicate differences in the mechanism of foveal hypoplasia in these two conditions. However the distribution of retinal vessels in the patients described by van Genderen *et al* was also different from that in albinism.

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Against this retrograde hypothesis is the observation that patients with incomplete congenital stationary night blindness show a degree of visually evoked potential (VEP) asymmetry indicating chiasmal misrouting, but of a lesser degree than is typical in albinism. They do not have foveal hypoplasia.⁵ Also Dorey *et al* reported three subjects being investigated for albinism, who showed VEP evidence of misrouting, but did not have clinical foveal hypoplasia.⁶ It is possible that lesser degrees of misrouting allow enough axons to acquire synaptic targets to permit foveal development. Alternatively it may be that some other primary defect can cause both foveal hypoplasia and chiasmal misrouting, but not necessarily together.

Both the sequence of normal development and evolutionary data may be of relevance. The first clear signs of non-uniformity of the posterior pole during development are the appearance of a central thickening of the ganglion cell layer and migration of photoreceptors, both of which have been described at 22 weeks of gestation in humans.⁷ As van Genderen *et al* note, this is well after chiasmal development is complete.