EDITORIAL

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Molecular genetics of eye diseases: where to go from here?

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The eye of the vertebrates has been known for more than 30 years to be formed by the complex interactive processes of molecular and cellular development of the neural and surface ectoderm.[1] The intriguing interactive induction between cells is mediated by a large signal transduction mechanism and involves a wide variety of signaling molecules and receptor proteins.[2] The G-protein coupled receptor system in the compound eyes in fruit flies provides one of the clearest signaling pathways in the regulation of eye development.[3] These biological developments are all essentially governed by genes. Genes that are defective due to sequence aberrations or hypermethylation, which lead to loss of normal function, are a primary cause of a number of single-gene-determined eye diseases.[4-7] Other eye diseases have a polygenic and multifactorial etiology, attributable to a multitude of interactive genetic and environmental factors.[8-10]

Such etiological complexity is well illustrated by age-related macular degeneration (ARMD), which is one of the most common causes of visual loss among the elderly in developed countries.[11] Risk factors for ARMD include age, smoking, intake of saturated fat and exposure to sunlight.[12-14] A genetic component of ARMD is highly likely, since family history is a risk factor.[15] In America, the prevalence of ARMD is higher in non-Hispanic whites than non-Hispanic blacks.[16,17] It is the leading cause of blindness in whites but not in blacks.[18] Age-related macular degeneration is pan-ethnic, but its prevalence in elderly Chinese appears to be lower, although we need more concrete data to support this clinical impression.[19] Recent advancement in the molecular genetics of ARMD may throw light on its genetic heterogeneity. Age-related macular degeneration and Stargardt disease are reported to be caused by mutations in the ATP binding transporter gene (*ABCR*), which is a large gene containing 50 exons and spanning 150 kb on chromosome 1p21-22.1.[20,21] It expresses exclusively and at high levels in retinal rod cells but not in cone photoreceptors. At least 25 *ABCR* mutations have been identified.[21] Age-related macular degeneration is a polygenic disorder. Since the apolipoprotein E gene (*APOE*) is also a potential susceptibility gene, the expression of ε2 allele increases, but the ε4 allele decreases, the risk for ARMD.[22,23] A linkage study from a large family with a dominant trait of ARMD enabled the mapping of the *ARMD1* gene on chromosome 1q25-q31.[24] Further molecular investigation should enable better understanding of the etiology of ARMD and a genotype-phenotype correlation analysis.

Myopia is another eye disorder with ethnic differences in prevalence. It is the most common eye disorder of the Chinese population in Hong Kong.[25] It is far more common in local Chinese than in Caucasians at all ages, after adjustment for ocular and metabolic disorders that are associated with

myopia.[10,11,26,27] Although environmental factors have been implicated, such a strong ethnic difference must be attributed at least in part to genetic predisposition, but the molecular genetics of myopia is still poorly understood. Familial myopia is transmitted in both autosomal dominant and recessive modes. The gene leading to myopia has not been identified. However, a recent genome-wide search has shown two possible loci, on chromosome 18p11.31[28] and 12q21-23,[29] suggesting that myopia is potentially a multifactorial and polygenic disease.

Rapid developments in molecular and cellular biology techniques over the last decade have contributed to the identification of genes and their mutations responsible for many ocular disorders. This genetic information also illustrates the complexity of the molecular genetics and pathogenesis of eye diseases.[30] The concept of a tumor suppressor gene, which inhibits cell growth and proliferation, was first described for the retinoblastoma gene, *Rb*.[31] The *Rb* protein is involved in suppression of cell growth through a phosphorylation and dephosphorylation mechanism. Deleterious *Rb* mutations are mostly in the germ line, and a mutated *Rb* gene leads to nonfunctional *Rb* variants, which stimulate cell proliferation. The *Rb* protein is also a target for DNA tumor virus oncoproteins, and association of the oncoprotein with an *Rb* mutant protein may also adversely affect normal *Rb* functions.[32]

From the clinical point of view, the therapeutic values of disease-causing gene mutations should be ascertained through large scale genetic studies. Are there DNA polymorphisms that can serve as genetic markers with agreeable sensitivity and specificity for detection of carriers in high-risk families? What are their values as prognostic indicators? Can response to different treatment modalities be predicted in carriers of specific mutations? Although the multifactorial nature of most eye diseases complicates matters, detailed and large-scale studies are under way with a view to providing answers to these questions for specific eye diseases. Meanwhile, genes responsible for many ocular diseases are still to be identified. It is expected that molecular studies of ARMD and myopia in the Chinese population in Hong Kong, based on their variation in severity and prevalence from other populations, will contribute immensely to the understanding in the etiology of these two diseases.

Research on eye genetics poses challenges to both clinical ophthalmologists and basic scientists. It will, inevitably, be a fruitful endeavor and will lead to advancement of basic knowledge and utilization of such information for clinical application, despite the complexity of the clinical, molecular and cellular aspects of eye diseases.

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