Myopia

Refining the aetiology of myopia through negative results

C A McCarty

Negative data help researchers to further refine the directions to identify the pathogenesis of myopia

Uncorrected or undercorrected refractive error is the leading cause of preventable vision impairment in the world today, with an estimated 75 million cases of low vision due to refractive problems.[1] Because refractive error is a major cause of avoidable blindness, the World Health Organization has named refraction as one of the five priorities for Vision 2020—the Right to Sight.[2] Not all blindness associated with refractive error is avoidable as high myopia can lead to choroidal atrophy and subsequent myopic retinal degeneration.[3]

People with myopia are more likely than people with hypermetropia to have undercorrected refractive errors.[4] Although debate continues about the relative contribution of genetics and environment in the development of myopia, there is general consensus that myopia has become more common[3] and indeed meets the definition of an epidemic: ''the occurrence in a community or region of … health-related events clearly in excess of normal expectancy.''[5] Some therapeutic interventions for myopia have been tested, but have been largely unsuccessful.[3] A better understanding of the causal mechanisms in the development of myopia is necessary to identify strategies for primary prevention.

In this issue of the *BJO* (p 5), Lee and colleagues question the postulated role of intraocular pressure (IOP) in the pathogenesis of myopia, based on their results from a cohort study of children in Singapore. Given conflicting data in the medical literature, how does a busy ophthalmologist respond to questions related to these research results from patients and what is the public health significance of these data?

Causal criteria can assist scientists and clinicians in the evaluation of epidemiological associations for non-communicable diseases.[6] Although not perfect, these causal criteria are useful for considering the importance and clinical relevance of findings from a single study in the context of previous research. The causal criteria include: (1) strength of association, (2) consistency of findings, (3) specificity, (4) temporality, (5) plausibility, (6) biological gradient (dose response), (7) coherence, (8) experimental evidence, and (9) analogy. One issue that makes it difficult to accurately synthesise research findings is publication bias, the tendency for negative study results not to be published.

The epidemiological criteria for causality can be used to consider Lee *et al*'s research findings and potential implications for education of patients with dissemination of these research results via the internet and/or media releases. Earlier studies have yielded conflicting data, and none has been able to adequately address the issue of temporality. Strengths of the current study include the standardised examination procedures, high response rate, and control of the major risk factor for myopia (genetics) by selection of an ethnically homogeneous population. The data displayed graphically in the figures show quite convincingly that not only is there no statistically significant relation between IOP and refraction or axial length, but also there is no suggestion of a non-significant trend or dose-response relation. These data tip the balance of consistency towards acceptance of the null hypothesis, at least for Chinese children. A meta-analysis may be in order to confirm this suggestion by statistically combining the results from all previous studies and would have been a useful addition to the current paper.

In summary, within the context of the causal criteria, the data from Lee *et al* do not support the use of ocular hypotensives to delay myopia progression in Chinese children. This same research group published negative results in 2001 resulting from their evaluation of the role of night lighting in the development of myopia in this same group of schoolchildren.[7] We applaud the authors for reporting their negative data because negative data help researchers to further refine the research directions to identify the pathogenesis of myopia, a very important research area given the global epidemic of myopia and associated low vision.

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Cataract

Understanding the molecular genetics of congenital cataract may have wider implications for age related cataract

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Treatment to slow down the progression of cataract would have a significant effect on the demand for cataract surgery

Congenital cataract, although uncommon, accounts for about 10% of childhood blindness.[1] The cataract is usually seen as an isolated abnormality but may occur in association with other ocular developmental or systemic abnormalities. About 50% of bilateral cases have a genetic basis. Congenital cataract is both clinically and genetically heterogeneous; isolated congenital cataract is usually inherited as an autosomal dominant trait although autosomal recessive and X linked inheritance are seen less commonly.[2] Most progress has been made in identifying the genes causing autosomal dominant congenital cataract.[2] Two main approaches have been used to identify the causative mutations. In large families linkage analysis has been used to identify the chromosomal locus followed by screening of positional candidate genes; most genes have been identified using this strategy. A second approach has been to screen DNA from large panels of patients with inherited cataract for mutation in the many candidate genes available.

The α, β, and γ-crystallins are stable water soluble proteins which are highly expressed in the lens; they account for about 90% of total lens protein, have a key role in lens transparency, and thus represent excellent candidate genes for inherited cataract.[3] α-Crystallin is made up of two polypeptides αA and αB encoded by the *CRYAA* gene on chromosome 21q22.3 and *CRYAB* gene on 11q22–q22.3, respectively. In addition to its structural role α-crystallin also functions as a molecular chaperone within the lens and other tissues.[4] Mutations in both *CRYAA* and *CRYAB* have been identified in families with ADCC[2 5] and in one family with a missense mutation in *CRYAB* affected individuals had both cataract and an associated desmin related myopathy presumably caused by impaired chaperone function of the mutant protein.[6] A nonsense mutation in *CRYAA* has also recently been reported in a consanguineous family with autosomal recessive cataract.[7]

The γ-crystallin gene cluster on chromosome 2q33–35 encompasses genes *γA* to *D* but only *γC (CRYGC)* and *γD(CRYGD)* are highly expressed in the human lens. Missense mutations in both genes have been identified in families with ADCC exhibiting a range of different phenotypes. Two different missense mutations within *CRYGD* (R36S and R58H) are associated with a crystalline-like cataract[8 9] and functional studies suggest that this may be due to reduced solubility and increased likelihood of crystallisation of the mutant protein.[10] The β-crystallin family encompasses four acidic (A) and three basic (B) forms encoded by genes on chromosomes 2, 17, and 22. Four mutations have been reported in the β-crystallin genes. Two different splice site mutations have been reported in the *CRYBA1* gene on chromosome 17q11.2 associated with nuclear and pulverulent phenotypes[11 12] and a *CRYBB1* nonsense mutation has been reported in a family with pulverulent cataract.[13]

A missense mutation in *CRYBB2* (Q155X) has been identified in three unrelated families with ADCC[14–16]; interestingly, the phenotype in each family is very different despite the identical mutation indicating that other modifier genes are likely to influence the cataract phenotype. Such modifier gene influences have recently been identified in a recessive murine cataract and it is likely that similar gene-gene interactions will be identified in human cataract.[17]

At least 15 different mutations in the crystallin genes have now been implicated in human cataract associated with a diverse range of phenotypes. It is still unclear what proportion of inherited cataract is associated with crystallin gene mutations as few studies have involved systematic screening of all crystallin genes in a large patient population. Burdon *et al* in this issue of *BJO* (p 79), however, report the results of one such study. They have used both linkage analysis and candidate gene screening to investigate the molecular pathology of inherited cataract in 38 families with AD and AR inherited cataract ascertained in southern Australia. They confined their investigation to five crystallin genes previously implicated in inherited cataract. Surprisingly perhaps, only two mutations (both of which have been described previously), a missense mutation (P23T) in *CRYGD* and a splice site mutation in *CRYBA1/A3*, were identified in the 38 pedigrees. Crystallin gene mutations at least in this specific population are an uncommon cause of inherited cataract.

There are a large number of potential candidate genes for inherited cataract and to date mutations have been identified in genes encoding various members of the crystallin family, membrane proteins including lens connexins,[18–22] aquaporin 0 (MIP)[23] and LIM2,[24] the cytoskeletal protein, beaded filament structural protein 2 (BFSP2)[25 26] and the transcription factors PITX3,[27] HSF4,[28] and MAF.[29] Very few mutations have been reported in each gene which suggests that that none of the genes so far identified accounts for a significant proportion of inherited cataract. It appears that inherited cataract is genetically very heterogeneous but given the paucity of studies that have screened all known cataract genes in a panel of carefully phenotyped patients it is still uncertain whether one or more genes may account for a significant proportion of cases.

> Is it really worth investing in this expensive genetic research when we have a very effective treatment for age related cataract? The answer must be yes

The identification of the genetic mutations underlying congenital cataract and subsequent functional studies will improve our understanding of normal lens development and the mechanisms of cataractogenesis. This information, although important, is unlikely to lead to any major clinical advance in the prevention of or management of congenital cataract as the cataracts in this young age group are usually present from birth. The importance of this type of research is in its implications for the more common age related cataract. Sibling and twin studies suggest that genetic factors play an important part in the aetiology of age related cataract.[30 31] The genes implicated in monogenic forms of cataract are good candidate genes for age related cataract. The pathogenesis of such cataracts is, however, likely to be complex

with age, genetic background, environmental exposures, and other disease associated risk factors such as diabetes all involved. It remains a major challenge, given these complex interactions, to identify the genes involved.[32]

Is it really worth investing in this expensive genetic research when we have a very effective treatment for age related cataract? The answer must be yes. Cataract remains the commonest cause of blindness worldwide and although surgical treatment is associated with excellent visual outcomes the demand for surgery exceeds the ability of most healthcare systems to deliver timely treatment. This problem is likely to worsen as the incidence of cataract increases as a result of demographic changes with the elderly making up a greater proportion of the population. Treatment to slow down the progression of cataract would have a significant effect on the demand for cataract surgery but prevention strategies depend upon an understanding of disease aetiology and need to be targeted at those individuals at greatest risk. An understanding of the genetic sequence variants that confer an increased risk of developing cataract holds the key to developing a medical treatment.

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