Editorial

Decoding retinitis pigmentosa

Dear Friends

Welcome to the next issue of Indian Journal of Ophthalmology (IJO)! After the successful introduction of monthly issues and the photo essays, I am happy to announce my next initiative – videos incorporated in the manuscript. I invite you all to submit videos along with your manuscripts for incorporation on the website and the link for the videos will appear on the print. This will provide a wonderful platform for learners as well as practitioners to interact and learn from experts on a variety of ophthalmic subjects. The technical specifications are: Acceptable file formats: mpg, mpeg, mp4, wmv, Max file size allowed: 20MB.

This issue deals with a plethora of subjects including retinitis pigmentosa (RP). RP and diabetic retinopathy (DR) sit at opposite poles in terms of genomic medicine. Genomic medicine is a newer off-shoot of medicine where interaction between entire genome of individual and non-genomic factors that result in health or disease is studied.[1] Great progress has been made in this area in the past 10 years and researchers are exploring how we could use this available knowledge in everyday circumstances and to the service of a patient. Obviously genomic medicine owes its existence today to the Human Genome Project,[2,3] HapMap Project[4,5] and Genome wide association study.[6,7] In this regard a series of articles, named 'Genomic Medicine series,'[8] that has been published by the New England Journal of Medicine (NEJM) since 2002 is a must read for the students of medicine. The latest article in this series has been published in 2010 in NEJM.[1]

Retinitis pigmentosa is usually a single gene disorder[8] while diabetes mellitus or DR have multifactorial (also known as polygenic or complex) etiology.[8] Single gene disorders are those disorders where single mutated gene is able to cause a clinical disorder. Multifactorial or complex disorders are those disorders where many genes partake in the development of a disorder but only under the influence of some unknown environmental and other factors.[8] It effectively means that two individuals may carry the same disease producing genes but one may develop the disease and the other may not develop the disease depending upon exposure to different environmental factors or different life-styles. Genome wide association study has provided some very fascinating insights in the understanding of complex disorders but the task has only just begun.[1,6,7]

Impressive advances have been made in the understanding of the pathophysiology and molecular insight in both RP and DR in the past decade, but the real challenge is how we can translate these advancements into management modalities.[9-11]

Burden of RP, which is the most common of inherited retinal dystrophies, in Indian society, is well-studied. Based on various publications in the past, prevalence of RP is estimated 1 in 4000 in western populations.[12-14] Sen *et al*.[15] has estimated presence of RP approximately 1 in 930 of urban while 1 in 372 of rural general South Indian population, aged 40 years or above. A much higher prevalence in South Indian population compared to western populations and population in the other parts of India has been noted. Social ills of consanguineous marriages in India must be brought forward in this context. In a very important publication, Kumaramanickavel *et al*.[16] has explored the influence of consanguinity on the prevalence of visual disorders in 2,335 patients attending a specialist genetic eye clinic in South India although study subjects were drawn from all over India. A total of 673 (28.8%) of the patients tested for ophthalmic genetic disorders reported a family history of consanguinity. South Indian families (574 families out of 673 such families) were accounted for the majority of such union. Among the consanguineous families, 430 of 673 (63.9%) had RP. Nirmalan *et al*.[17] has also studied the effect of consanguinity on eye diseases with potential genetic etiology in Andhra Pradesh. These figures underline the urgent need for highlighting the problem of RP in India and the subcontinent. The burden of making our society aware of the ills of consanguineous marriages lays with us ophthalmologists only.

Many efforts have been made in preventing or slowing the visual loss or disability in RP in the past, but our efforts have been limited by the poor understanding of the pathological or molecular events of the disorder. Recent genetic insights have provided much needed input for the development of treatment modalities.[18,19] Since the first reported mutation associated with RP in humans by Dryja *et al*.[20] in 1990, 26 genes for autosomal recessive (AR) RP and 20 for autosomal dominant (AD) RP, and 2 genes for the X linked RP has been identified until 2010.[21] Genetics of RP is much more complex than it was initially believed with more than 200 genetic loci for various genes and with evidence of digenic, mitochindrial RP where altered genes for RP occur on 2 different chromosomes in the same individual and in mitochondrial DNA respectively. Triallelic form of RP has also been reported. In approximately 50% of RP cases, no genetic cause is identified.[21-23]

On the management front, now gene therapy and cell transplantation experiments are offering fresh hope for prevention of blindness and retarding the disease progression.[24] Though Berson *et al*.[25] in their study has reported slower rate of ERG reduction in common forms of RP and Usher syndrome in adults by supplementation of very high doses of vitamin A (15,000 IU/day) through some unknown mechanism while vitamin E was noted to cause deterioration. Critically reviewing, ERG measurements as endpoint to evaluate the effect of a drug certainly have limitations, and it may not represent the true functional and visual status of a patient. This aspect of the study has been extensively discussed by Massof and Finkelstein[26] in their editorial in the Archives of Ophthalmology in June 1993. Further, Berson *et al*.[27] in 2004 have published results of their trial evaluating roles

of docosohexanoic acid (DHA) with vitamin A on the progression of visual field loss in RP. In 2010 Berson *et al*.[28] published their third trial results of the effects of lutein with high dose of vitamin A and high dietary intake of DHA on the progression of visual field loss in RP patients. In all these 3 trials, visual acuity or visual functions were not taken as study end points. Editorial in the April 2010 issue of Archives of Ophthalmology,[29] which has published the trials, has collectively discussed about merits and demerits of these 3 trials by Berson *et al*. I am also not in favor of using high doses of vitamin A for such a long period of time with no effect on visual outcome. Though, the National Eye Institute (NEI) reaffirmed its recommendation for vitamin A supplementation for adult patients with common forms of RP in July 2008.

Gene therapies or cell transplantation therapies aim at the correction of defective genes or its effects in an organism,[30,31] at least in theory which make these approaches attractive. Currently gene therapies are centered on one of three methods:

1. Insertion of a normal gene into the genome to replace nonviable or diseased genes using a carrier "vector," with or without knockout of the defective gene,[31,32]
2. Ribozyme therapy, and
3. RNA interference

First approach is almost necessary in AR conditions while other two are appropriate for AD disorders. Sometimes we need to knock out the mutated genes even after the successful introduction of healthy genes through separate vectors because the presence of abnormal protein products of mutated genes interfere with the functioning of normal protein products of newly introduced genes. Gene replacement therapies rely heavily on the adeno associated virus (AAV) vector to introduce healthy genes in a cell. AAV are non-immunogenic and its genome does not incorporate in the genome of host cells (code proteins independent of the host genome as circular DNA) thereby avoiding the chances of iatrogenic mutations or neoplasm. AAVs are small viruses and cannot carry large segments of genetic materials within them.[32] Gene replacement through vectors have experimentally been shown to delay and even reverse the course of RP with associated improvement of photoreceptor function in various animal models.[30,32,33]

Ribozymes destroy the abnormal RNA molecules arising from the mutated genes[34] while in RNA interference techniques, micro RNA (mi RNA) or interfering RNA (si RNA) segments inactivate RNA molecules by binding with them.[35]

Retinal or stem cell transplantation to replace damaged cells of the retina and restore visual function is being actively studied. Sheets of fetal retinal cells can morphologically repair an area of a degenerated retina, and there is evidence to suggest that transplants form synaptic connections with the host and restore visual responses in blind rats.[36,37] Arai *et al*. have noted visual responses to a light flash across the superior colliculus in *rd* mice.[37] Radtke *et al*.[38] transplanted a sheet of fetal neural retina with its retinal pigment epithelium into the subretinal space under the fovea unilaterally in a patient with RP with visual acuity of 20/800 in the treated eye and reported visual improvement of 20/160 at 1 year in this patient. In another very important work Radtke *et al*.[39] have demonstrated the long term (upto 6 years) safety of transplanted sheet of fetal neural retina with its retinal pigment epithelium into the subretinal space in one eye of the 10 patients (6 RP and 4 age related macular degeneration), 7 patients (3 RP and 4 age related macular degeneration) were observed to have visual improvement.

So far, brain- and retina-derived stem cells transplanted into adult retina have shown little evidence of being able to integrate into the outer nuclear layer and differentiate into new photoreceptors.[40] However, Qiu *et al*.[41] and Klassen *et al*.[42] in their respective work have shown that transplanted retinal progenitor cells in animal models were able to express photoreceptor markers and show photoreceptor differentiation and integration into allorecipients' retina. On the other hand, Chacko *et al*.[43] have noted that transplanted retinal stem cells into the subretinal space of the degenerating retina in an animal model; exhibited preferential expansion as ganglion and glial cells rather than photoreceptor cells.

Here, it must be pointed out that these advances look very promising and exciting but a majority of gene therapy or cell transplantation efforts are still at *in vitro* experiment level and the rest are at animal studies level. Results from a small group of patients as reported by Radtke *et al*.[38,39] need further validation.

Role of genetic counseling cannot be undermined in the management of hereditary retinal dystrophies. The aim of genetic counseling is to help patients make informed decisions regarding marriage, pregnancy, job selection or further management of their condition by explaining patients the hereditary nature of their eye disease and the likely mode of inheritance based on pedigree analysis and genotype (if known) as well as the likelihood of the trait expressing itself in other family members or future generations. The first requirement of genetic counseling is the exact clinical diagnosis of the patients' conditions.[23,44] This very well explains why we must take care of these patients and their family members very carefully with very elaborate history taking and examination to establish accurate clinical diagnosis. This little effort of ours goes a long way in helping patients and securing their future and in reassuring their aggrieved family members.

The National Eye Institute, in consultation with leading clinicians, scientists, genetic counselors and ethics/policy experts, has created the National Ophthalmic Disease Genotyping Network or eyeGENE™ to face the challenges of hereditary retinal dystrophoies. Since the start of its operations in September 2006 eyeGENE™ network has grown substantially. The eyeGENE® Network is made up of a group of vision research and clinical labs located across the United States and Canada, a Coordinating Center located at NEI in Bethesda, a bank of blood/DNA samples, and a secure online database. The eyeGENE™ network receives blood and DNA samples from the patients and/or family members from all over the world and offers genetic tests and its services free of cost to them but does not bear sample collection or shipping costs. Genetic tests for the unborn child are also not provided by eyeGENE™.[45]

In this issue of IJO Tawada *et al*. has evaluated the effect of topical isopropyl unoprostone on central retinal sensitivity in RP patients. As I mentioned earlier, in this study also, visual acuity or functions have not been taken as study end points. Furthermore, authors have only measured sensitivities in central 2 and 10 degree of the retina. Sensory information from such a small area of the retina does not usefully incorporate with the overall sensory inputs from other parts of the body in the brain. What makes this study promising is the improvement in retinal sensitivity in the study eyes after the application of topical isopropyl unoprostone. After discussing the complexities involved in the approaches of gene therapy and cell transplantation, a successful outcome in RP patients only by ocular topical application of an agent is highly encouraging and promising for everyone. There is light at the end of a long tunnel for managing patients with RP and a lot of work to be carried out before we reach there!

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