Trials and tribulations of rare eye diseases

Rare diseases (RD) have emerged as one of the key public health concerns recently. This implies that despite the rarity of these diseases as per definition, a significant amount of people, in millions, are affected worldwide. Diseases are currently classified as RD based on their reported prevalence centered on epidemiological data, and it ranges between 1/10,000 and 10/10,000 affected individuals in a given population, as per the World Health Organization (WHO) and independent data from different countries.[1] Regrettably, the lack of epidemiological data of RD in India does not provide the magnitude of disease burden caused by them among Indians. Majority of RD are inheritable and have strong genetic predisposition and mutations toward the causality. Since India is one of the countries with high rates of consanguinity, the prevalence could be higher than in other countries. Rare eye diseases (RED) contribute substantially to the list of RD, with close to 1000 RED conditions.[2,3] Ocular structures affected by RED include cornea, retina, optic nerve or the entire eye globe. RED-associated morbidity affects the quality of life (QoL) of patients and carers markedly, contributing to significant psychological and economic burden.

Ophthalmologists have been serving relentlessly to create a world free of visual impairment, and RED poses a number of challenges in achieving the goal of quality vision for all. The reasons underpinning high incidence and morbidity associated with RED include (i) delay in confirmatory diagnosis, (ii) lack of knowledge on the detailed mechanisms associated with the pathogenesis, (iii) dearth of treatments and targeted therapies, and (iv) paucities in public awareness about inherited diseases. Early and accurate diagnosis would enable the patient to engage in health practices that can result in slowing down of disease progression, preparedness, skill development to improve QoL, and participate in emerging therapies or clinical trials. The delays and hurdles to arrive at accurate and early confirmatory diagnosis of RED are due to lack of access for these patients to specialist care including affordable genetic testing. Detailed mechanistic knowledge underlying the pathogenesis of RED will provide insights into cellular and molecular pathways that may be shared by RED and other relatively well-understood common eye diseases with varied therapeutic strategies which can be harnessed in RED. The lack of mechanistic knowledge is due to rarity of the condition, which makes it challenging to access biological materials for detailed cellular/molecular studies and development of animal models. Despite early and accurate diagnosis, the absence of therapies contributes to continued morbidity and disease burden in many RED patients. This is a very disconcerting situation across RD as well, with more than 95% of RD having no approved treatment.[4] It is widely accepted that RED can be better managed with targeted and personalized therapies. In this context, gene therapy has evolved as one of the most promising and successful treatment strategies for a variety of RD. More recently, the first gene therapy (adeno-associated virus based) for the treatment of Leber congenital amaurosis-2, a RED, has been approved for clinical use.[5] The technological bottlenecks in the development of such therapies slow down their rapid development and render them unaffordable for many. This is further complicated by the differences in the disease-causing mutations or genetic variations among different ethnicities. One of the critical contributors toward the prevalence of RD is the lack of awareness among the general public, particularly in societies with higher frequency of consanguineous marriages, regarding the heritable nature of these conditions.

The action plan to reduce the prevalence of disease burden of RED addressing the four major formidable challenges listed earlier is as follows. Early and accurate diagnosis can be improved by (i) capacity building with a trained multidisciplinary team and infrastructure capable of detailed documentation of clinical phenotypes and genotypes associated with RED; (ii) identification of tertiary eye care centers, state or district wise, as nodal centers that can provide capacity for the diagnosis of RED; (iii) development of national registries for RED with detailed genotype and clinical information that would be accessible to all nodal centers, as this will be useful to determine ethnicity-specific genetic variation in RED; (iv) development of public–private sector partnership to make genetic testing more affordable; (v) easy availability of panels such as the Oculome to facilitate the diagnoses of a range of genetic conditions affecting the eye;[6] (vi) conducting periodic expert group meetings to develop consensus and update clinical and genetic information associated with RED, and (vii) having representatives for RED (ophthalmologists) to work with government policymakers addressing RD in the country.[7] Detailed mechanistic knowledge about the pathogenesis would be improved with focused research efforts. It would include (i) creation of biorepositories to collect and store RED tissues, (ii) disease modeling using animal models or organoid models with induced pluripotent stem cells (iPSCs) derived from RED patients, and (iii) funding and participation by all the stakeholders in this attempt. Development of treatments, such as gene therapy, in India would profoundly reduce the disease burden in India. It is important to note that there are national guidelines for gene therapy product development and clinical trials[8] to facilitate the development of targeted and affordable gene therapy. The various action plans discussed above, right from making genetic testing more affordable to development of registry to improve knowledge regarding disease mechanisms, would directly impact the development of next-generation therapeutics, such as mutation-specific and mutation-independent gene and cell therapies, for the treatment of RED. Finally, increasing public awareness about RED and inherited disease would substantially reduce the prevalence of RED and the associated disease burden. This can be addressed effectively and sustainably by (i) encouraging genetic counseling and making it accessible by the creation of trained genetic counselors in health-care establishments and (ii) creating consortium for RED that would include all the stakeholders – such as patients, caregivers, ophthalmologists, geneticists and industry personnel (genomic technology and biopharmaceuticals), philanthropists, and policymakers. Addressing the major challenges by the discussed approaches would collectively and substantially reduce the cumulative burden of RED on the affected and health-care systems.

This special issue on "RED," through its many articles by experts, intends to communicate the contemporary

understanding of RED with reference to clinical spectrum, genetic/molecular basis of disease pathogenesis, and emerging management strategies. The contents of the issue will aid to address the challenges posed and implement the action plans to substantially increase the rarity of RED and improve the QoL of those with RED. With ever-growing trained multidisciplinary teams, technological advancements, and awareness, we are well poised to reduce the burden rendered by RED, by narrowing the gap between RED and management solutions.

Rohit Shetty, Swaminathan Sethu[1], Chaitra Jayadev

Department of Ophthalmology, Narayana Nethralaya Eye Institute, Bengaluru, Karnataka, [1]GROW Research Laboratory, Narayana Nethralaya Foundation, Bengaluru, Karnataka, India.
E-mail: drchaitra@hotmail.com

References

1. Richter T, Nestler-Parr S, Babela R, Khan ZM, Tesoro T, Molsen E, *et al.* Rare disease terminology and definitions-A systematic global review: Report of the ISPOR rare disease special interest group. Value Health 2015;18:906-14.
2. Sergouniotis PI, Maxime E, Leroux D, Olry A, Thompson R, Rath A, *et al.* An ontological foundation for ocular phenotypes and rare eye diseases. Orphanet J Rare Dis 2019;14:8.
3. Black GC, Sergouniotis P, Sodi A, Leroy BP, Van Cauwenbergh C, Liskova P, *et al.* The need for widely available genomic testing in rare eye diseases: An ERN-EYE position statement. Orphanet J Rare Dis 2021;16:142.
4. The Lancet Diabetes Endocrinology. Spotlight on rare diseases. Lancet Diabetes Endocrinol 2019;7:75.
5. Askou AL, Jakobsen TS, Corydon TJ. Retinal gene therapy: An eye-opener of the 21st century. Gene Ther 2021;28:209-16.
6. Patel A, Hayward JD, Tailor V, Nyanhete R, Ahlfors H, Gabriel C, Jannini TB, *et al*. The oculome panel test: Next-generation sequencing to diagnose a diverse range of genetic developmental eye disorders. Ophthalmology 2019;126:888-907.
7. National Policy fo Rare diseases. Ministry of Health and family Welfare, Government of India; 2021.
8. National Guidelines for Gene Therapy Product Development and Clinical Trials. Indian Council of Medical Research; 2019.

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About the author

Prof. Dr. Rohit Shetty, DNB, FRCS, PhD (Netherlands)

Dr. Shetty is a cornea-refractive surgeon and a clinician scientist with a keen interest in keratoconus and corneal ectatic disorders with a high volume refractive surgery practice. Dr. Shetty completed his residency in ophthalmology at the St. Johns Medical College for the Diplomate of the National Board. Dr. Shetty obtained his FRCS Glasgow, Scotland, United Kingdom in 2006 and is currently an FRCS examiner. He is the Chief Mentor for the Dual Academic Program (PhD and Clinical Fellowship) at Narayana Nethralaya Eye Institute, Bangalore and Maastricht University.

Dr Shetty has close to 300 publications in peer-reviewed journals and is a reviewer for many indexed journals in the specialty. He is also on the editorial board of the Journal of Refractive surgery. Dr Shetty's work on pain management after photorefractive keratectomy, influence of stromal molecular markers on corneal ectasia and risk scoring systems to predict ectasia after refractive surgery has been well received. With a keen interest in imaging, some of his research includes - waveform analysis of deformation and deflection amplitude in keratoconus, influence of ocular spherical aberration on near and intermediate visual acuity in presbyopic eyes, biomechanics of LASIK Flap and SMILE Cap and corneal tomography in post-refractive surgery ectasia.

In the 2015 annual conference of the All India Ophthalmological Society, Dr. Shetty won the prestigious Col. Rangachari Award for the overall best paper of the conference for his work on "Is Inflammation Driving Keratoconus? A Holistic Study of Molecular Pathways". The American Academy of Ophthalmology recently conferred an achievement award to him for the distinguished services he has rendered over the years to the programs of the society. He was awarded the Casebeer Award for outstanding contribution to refractive surgery by the ISRS in 2019. Recently, he was listed amongst the top 100 most influential ophthalmologists in the world and is in the top 2% scientists in the field as named by the Stanford University. Dr Shetty is also recognised among the top 10 keratoconus experts in the world. Dr. Shetty is a visionary leader, and truly a trailblazer translational researcher in ophthalmology in India, who has set very high benchmarks. He is an icon in Indian ophthalmic research and an inspiration to generations of young Indian ophthalmologists.