Global Eye Genetics Consortium

Newsletter #10

FOREWORD

Prof. Dr. S. Natarajan
Vice President of the Global Eye Genetics Consortium (GEGC)

As the Vice President of the Global Eye Genetics Consortium (GEGC), it is my honor to present this foreword, celebrating a transformative time in the field of human genetics and eye health. The rapid advancements in genome sequencing and computational technology have ushered us into a new era, one that holds immense promise for understanding and addressing eye diseases at their molecular origins.

Decades of rigorous research have established a clear link between genetics and the onset of ocular disorders. Whether through highly penetrant Mendelian variants or as contributing factors to more common eye diseases, the genetic underpinnings of these conditions are critical to understanding their development and treatment. In this era of precision medicine, our ability to sequence patient genomes rapidly enables us to trace these variants within families and patient cohorts, providing insights that were once beyond our reach. Yet, it is important to acknowledge that much of the genetic data currently available is derived primarily from populations in developed countries, leaving a significant gap in our understanding of eye diseases that affect diverse global populations.Founded in 2014 as the Asian Eye Genetics Consortium (AEGC) and subsequently expanded in

2018, the GEGC has been a beacon of collaboration, focusing on fostering partnerships in eye genetics research, particularly in developing regions of Asia, Africa, and Central & South America. Today, we are proud to have over 200 dedicated members—scientists and ophthalmologists—from 30 countries, all united by a shared mission to unravel the complex genetic landscape of eye diseases.

We are excited to announce the launch of the GEGC Phenotype-Genotype Database, "GenEye," an innovative platform to collect and analyze phenotype-genotype information. This resource will be instrumental in identifying genetic variants associated with diverse eye diseases, leading to improved diagnostics and therapeutics. Furthermore, GEGC is committed to organizing educational sessions at local and international ophthalmology meetings to advance knowledge and collaboration in our field.

To all those interested in advancing the field of eye genetics, I invite you to visit our ***"Join GEGC"*** page to register as an active member. Together, we can identify disease variants linked to genetic eye diseases and ensure that no population is left behind in our quest for knowledge and better health outcomes.

Through collaborative effort and innovation, the Global Eye Genetics Consortium stands poised to make significant contributions to the understanding and treatment of genetic eye diseases worldwide. I look forward to working alongside all of you as we embark on this vital journey.

Importance of Creating a Registry of Genetic Eye Diseases

In the rapidly evolving field of ophthalmology, the establishment of a comprehensive registry for genetic eye diseases is of paramount importance. Such a registry would serve multiple critical functions, notably in the realms of research, clinical practice, and patient management. By collecting and cataloging phenotype and genotype information, we can enhance our understanding of these complex conditions and improve the precision of diagnoses.

Standardization and Data Collection

Creating a registry facilitates standardized data collection related to genetic eye diseases. By systematically recording clinical phenotypes—the observable characteristics of patients—and genotypes—the underlying genetic variations—we can begin to establish robust correlations between specific genetic mutations and the clinical manifestations of these diseases. This information is essential for advancing our understanding of disease mechanisms and identifying previously unrecognized genetic variants that may play significant roles in the onset and progression of eye disorders.

Reconfirming Diagnoses Post-Genetic Testing

An integral aspect of a genetic registry is the ability to reassess and reconfirm diagnoses after genetic testing. Genetic testing alone is not always definitive; interpretations can vary, and the clinical context is critical for accurate diagnosis. A well-organized registry allows for integrated data analysis, enabling clinicians to review genetic findings alongside detailed clinical histories. This holistic approach enhances diagnostic accuracy and aids in identifying disease variants that may have been overlooked initially.

Facilitating Research and Collaboration

A genetic eye disease registry also serves as a vital resource for researchers and clinicians alike. It fosters collaboration among scientists, ophthalmologists, and geneticists within the Global Eye Genetics Consortium and beyond, promoting an environment where data sharing can lead to groundbreaking insights. By pooling genetic data and phenotype profiles, we can accelerate research into the epidemiology, progression, and treatment outcomes associated with various genetic eye diseases. This collaborative effort can lead to the

discovery of new therapeutic targets and personalized treatment strategies, ultimately benefiting patients worldwide.

Improving Patient Care and Management

With a comprehensive understanding of the genetic landscape of eye diseases at our disposal, we can develop more effective preventive strategies, targeted interventions, and tailored management protocols. The insights gained from registry data can inform clinical decision-making and guide the implementation of personalized care pathways based on a patient's specific genetic profile. This approach not only enhances the quality of care but also empowers patients with knowledge of their conditions and available therapeutic options.

Future Directions

As we work towards establishing a global registry for genetic eye diseases, it will be essential to focus on inclusion and representation from diverse populations. Genetics is not uniform; variations across different ethnic and geographic groups can significantly influence disease presentation and outcomes. By capturing diverse genetic data, we strive to address health disparities and ensure that advancements in genetic research benefit all communities.

In conclusion, the creation of a registry for genetic eye diseases is a crucial step in advancing our understanding of these complex conditions. It lays the groundwork for improved diagnostics, fosters collaborative research, and ultimately enhances patient care. Together, we can build a comprehensive resource that empowers both clinicians and patients, paving the way for innovative solutions in the realm of genetic ophthalmology.

RECENT EVENTS

Global Eye Genetics Consortium (GEGC) at APAO-AIOS 2025

Date: 04th April 2025 | Time: 16:45 – 18:00 hrs | Venue: Trade Room 5, Yashobhoomi, New Delhi, India
Theme: World Ophthalmology: Face to Face
Hosted by: Global Eye Genetics Consortium (GEGC)

The Global Eye Genetics Consortium (GEGC) convened a landmark international session during the APAO-AIOS 2025 meeting in New Delhi, bringing together experts from around the world to deliberate on the rapidly evolving landscape of genetic eye disease research and its clinical translation.

Chaired by Dr. S. Natrajan (India) and Dr. Calvin Pang (Hong Kong), the session reflected a blend of regional insights and global collaborations. Dr. Natrajan focused on recent advancements in gene therapy in India, highlighting progress in early-phase trials and collaborative infrastructure. Dr. Pang shared experiences from large-scale genomic cohort studies in childhood myopia, emphasizing the value of population-based data in understanding disease mechanisms and discovering biomarkers.

Dr. Namrata Sharma (India), serving as a chairperson, offered perspectives on India's unique clinical challenges in inherited eye diseases and the need for national genomic registries and translational pipelines.

Among the international speakers, Dr. Janey Wiggs (USA) presented on global collaborations in glaucoma genetics, underlining the significance of data sharing and harmonization across continents. Dr. Gerald Schultz (USA) provided an overview of current genetic treatments, mapping where we stand today in terms of approved therapies and emerging trials.

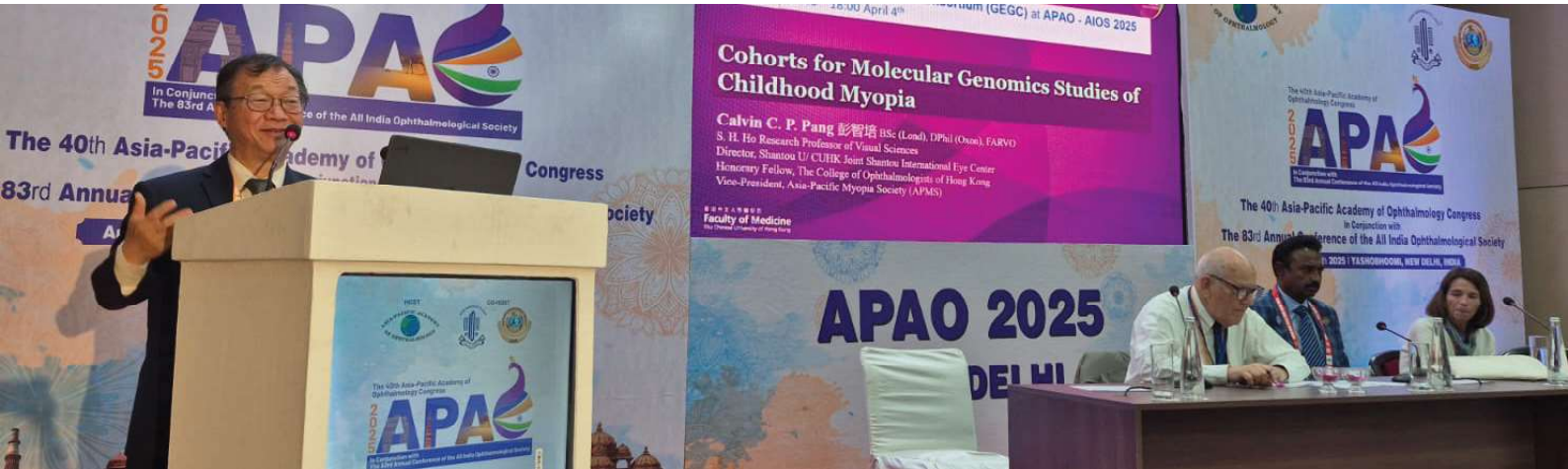
A highlight of the session was a video presentation by Dr. Anne Slavotinek (USA) on zebrafish models of structural eye defects. Her talk bridged basic science with translational potential, showing how developmental biology can inform diagnosis and therapeutic targets in pediatric ophthalmic disorders.

Dr. Viney Gupta (India) delivered a segment on the application of genetics in anterior segment disorders, drawing from clinical cases that integrate genetic diagnosis with surgical planning and management. Dr. Shailja Tibrewal's (India) topic was titled "Genetic Eye Diseases: A Clinician's Perspective", sharing insights into the diagnostic, counseling, and therapeutic challenges faced by frontline pediatric ophthalmologists when managing inherited ocular diseases.

The session emphasized:

- ***The critical role of collaborative international networks like GEGC in accelerating research.***
- ***The value of cross-disciplinary training for clinicians in genetics.***
- ***The need for robust funding and policy advocacy to support genetic services and rare disease research in low- and middle-income countries.***

This meeting underscored the urgent need for global partnerships and the integration of clinical genetics into ophthalmology practice, particularly in pediatric and complex eye disorders. The GEGC aims to continue fostering dialogue, research collaborations, and capacity-building efforts worldwide.



MEMBERS SPEAK

Gene Therapy and Artificial Retina in Ophthalmology

As we gaze into the future of ophthalmology, the potential of gene therapy and artificial retina technologies stands out as a beacon of hope for countless individuals affected by hereditary and degenerative eye diseases. Advances in these fields not only promise to revolutionize patient care but also reflect the remarkable progress being made in the realm of precision medicine.

Gene Therapy: A New Frontier

Gene therapy has emerged as a groundbreaking approach for the treatment of genetic eye diseases, particularly those stemming from mutations that disrupt normal retinal function. This innovative technique involves the introduction, removal, or alteration of genetic material within a patient's cells to correct or compensate for faulty genes responsible for specific disorders.

Among the most notable successes in this field is the use of adeno-associated viral (AAV) vectors to deliver healthy copies of genes directly into the retina. Treatments such as Luxturna for Leber Congenital Amaurosis have demonstrated promising results, restoring vision in patients with mutations in the RPE65 gene. As research continues, we anticipate the development of more targeted therapies that address a wider array of retinal diseases, including retinitis pigmentosa and age-related macular degeneration. Moreover, ongoing advancements in CRISPR technology open up new possibilities for gene editing, enabling precise modifications that could correct genetic defects at the source.

The Road Ahead

The integration of gene therapy and artificial retina technology signifies a paradigm shift in ophthalmology, reflecting a more personalized, patient-centric approach to eye health. As we continue to explore these avenues, collaboration among geneticists, ophthalmologists, engineers, and technology developers will be crucial in overcoming current challenges and enhancing treatment efficacy.

Moreover, ethical considerations, accessibility, and affordability will need to be addressed to ensure that these groundbreaking therapies are available to all who need them. Engaging with global partnerships, such as those fostered by the Global Eye Genetics Consortium, will be vital to share knowledge and resources, ensuring that advancements in gene therapy and artificial vision are felt around the world.

In conclusion, the future of gene therapy and artificial retina technologies is bright, poised to change the landscape of ophthalmology for generations to come. Together, we stand on the brink of a new era in vision restoration, where the combination of cutting-edge science and clinical application will unlock unprecedented opportunities for individuals with vision loss.

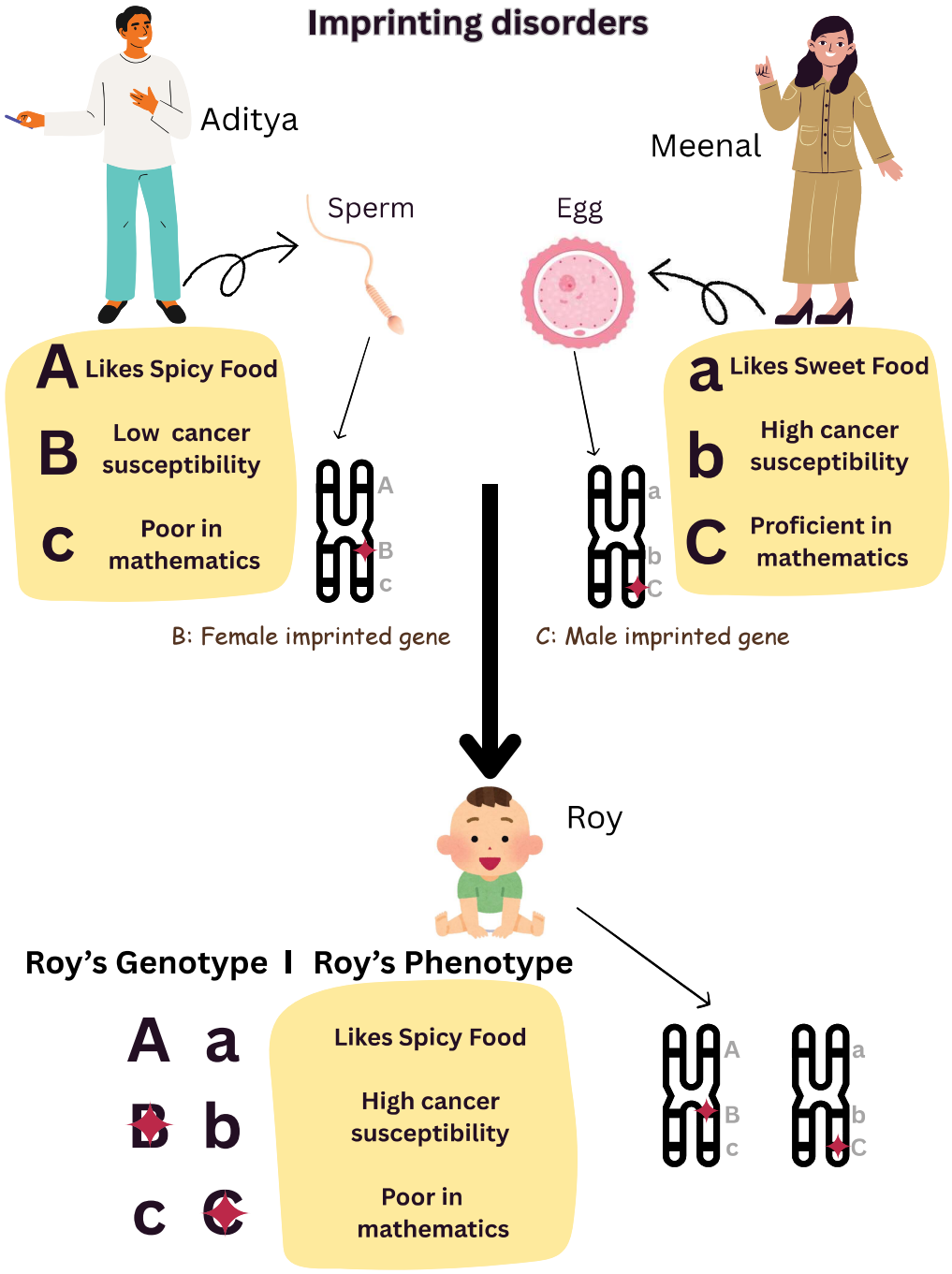
Artificial Retina: Restoring Vision to the Blind

In parallel with gene therapy, artificial retinal implants represent a revolutionary approach to restoring vision for those with advanced retinal diseases. These devices, often referred to as "bionic eyes," are designed to substitute for lost photoreceptor cells by converting light into electrical signals that can be interpreted by remaining retinal neurons. The Argus II Retinal Prosthesis System, for instance, has already provided functional vision to many patients with profound vision loss due to retinitis pigmentosa.

As technology evolves, future iterations of artificial retinas may integrate more sophisticated components, such as wireless connectivity and improved image resolution, potentially offering more natural vision restoration and adaptability to different lighting conditions. The development of closed-loop systems, which combine real-time image processing with sensory feedback, holds promise for an even more immersive experience for users.

Contributed by-
Prof. Dr. S. Natrajan

THE GENETICS 101



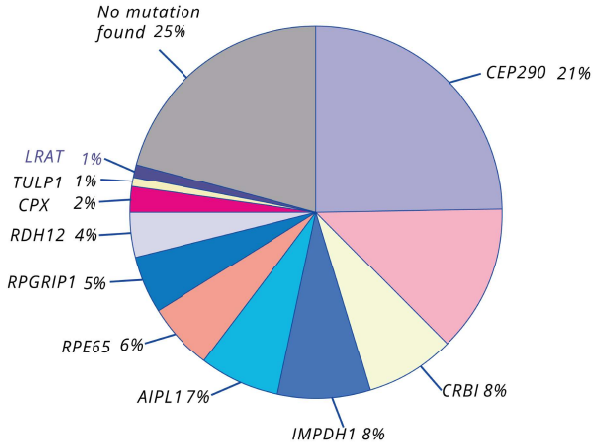
For this edition of Genetics 101, we have a visual snapshot explaining the concept of imprinting disorders—conditions caused by disruptions in the normal pattern of parent-specific gene expression. Unlike most genes, which are expressed from both maternal and paternal copies, imprinted genes are expressed from only one parent's allele. This tightly regulated process can be altered by genetic mutations, deletions, or epigenetic errors, leading to disorders such as Prader-Willi syndrome, Angelman syndrome, and Beck-with-Wiedemann syndrome. Understanding imprinting is crucial in both diagnosis and genetic counseling, especially for syndromes with overlapping features and parent-of-origin effects.

Ocular abnormalities, though variable, are observed in several imprinting disorders. Individuals with Angelman syndrome may present with strabismus, hypopigmentation of the iris and fundus, or refractive errors. In Prader-Willi syndrome, features such as myopia, strabismus, and abnormal visual tracking have been reported. While not always the primary concern, recognizing these ocular signs can aid early diagnosis and help guide multidisciplinary care in affected individuals.

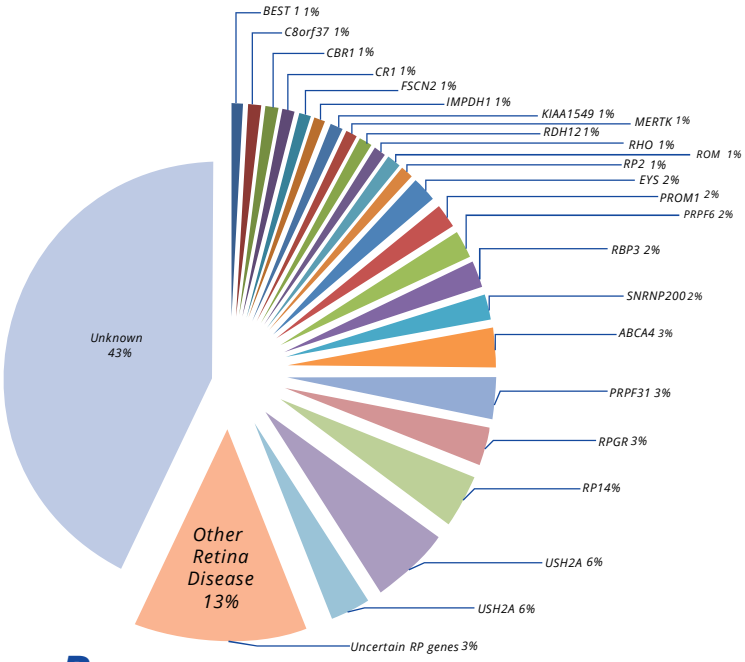
TRIVIA

Match the Mutation screening illustration *(A to D)* with the genetic disorder *(1-4)*

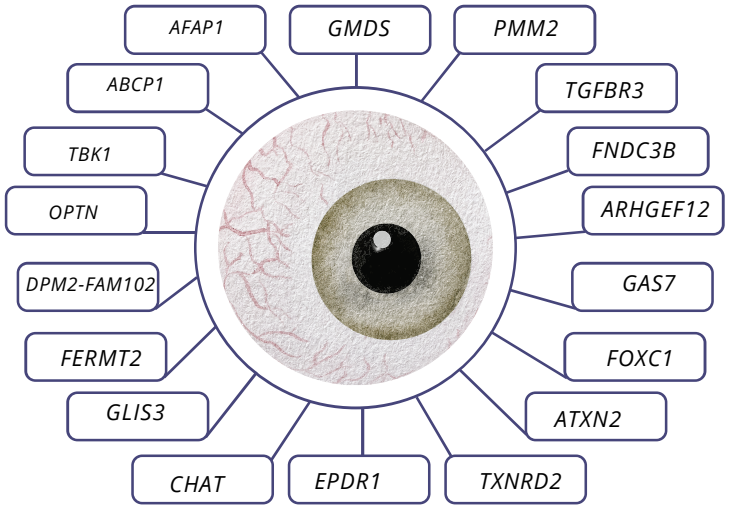
1. Retinitis pigmentosa
2. Leber's Congenital Amaurosis
3. Congenital Glaucoma
4. Congenital Cataract



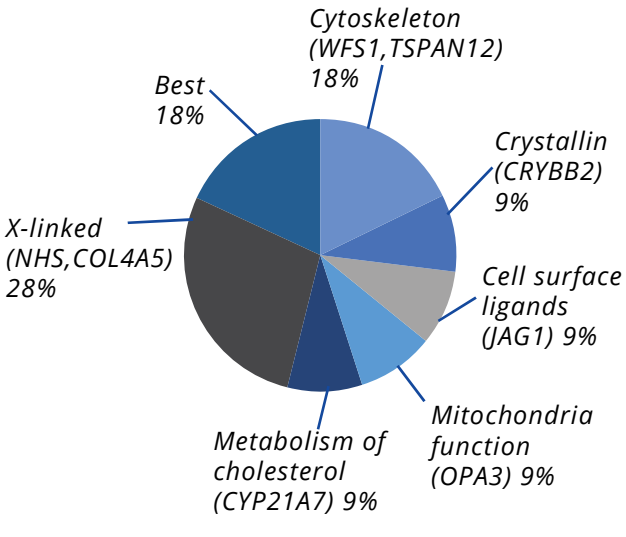
A



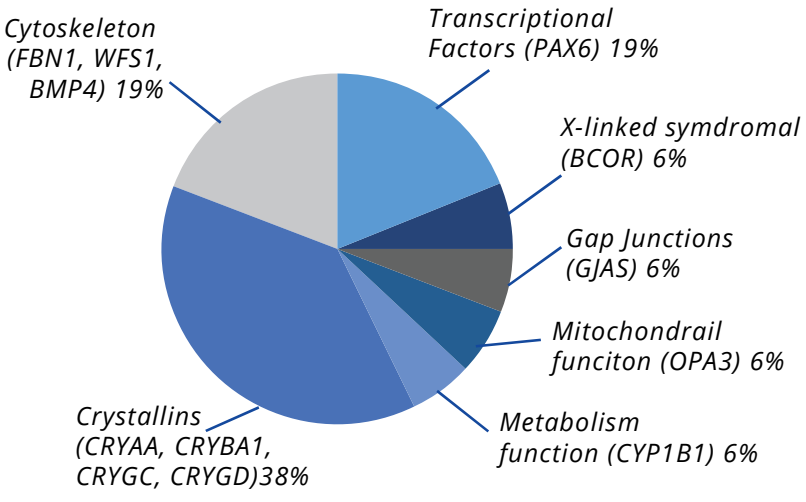
B



C



D ***Sporadic***



Familial

KNOW OUR MEMBERS

Dr. Tanmayi Dhamankar is a dedicated Paediatric Ophthalmologist and Strabismus specialist with over nine years of clinical experience. Her key areas of interest include the management of refractive errors and amblyopia, squint and nystagmus, neuro-ophthalmology, and genetic eye disorders. She recently completed a specialized short-term training in Ocular Genetics at Ghent University Hospital, Belgium, under the mentorship of the renowned Prof. Bart Leroy. With this achievement, she proudly holds the distinction of being Maharashtra's first ocular geneticist.

Dr. Dhamankar currently practices at Hemdeep Clinic, Navi Peth, and serves as a visiting consultant in Paediatric Ophthalmology and Ocular Genetics at several reputed eye hospitals across Maharashtra. In addition to her medical career, she is also a professional dancer and choreographer—bringing creativity, discipline, and balance to all areas of her life.

Prof. Salil A. Lachke is a researcher and educator specializing in molecular biology and organ development. He holds a B.Sc. and M.Sc. from the University of Pune, India, and earned his Ph.D. from the University of Iowa in 2003. After completing a postdoctoral fellowship at Harvard Medical School and Brigham and Women's Hospital, Dr. Lachke became an Instructor in Medicine at Harvard in 2011.

Dr. Lachke's research focuses on identifying and understanding genes involved in organ development and disease. His lab developed the bioinformatics tool "iSyTE" (Integrated Systems Tool for Eye gene discovery), which has been instrumental in discovering novel cataract genes and other genes involved in lens development. His research aims to define gene regulatory networks (GRNs) that control organogenesis, with the goal of developing new therapies for organ-related diseases. His work has been published in Science, Developmental Dynamics, PLOS Genetics, and Nature Communications.

In addition to his research, Dr. Lachke teaches Molecular Biology of the Cell (BISC401) and serves as a research advisor to both undergraduate and graduate students. His work bridges developmental biology and clinical applications, with a particular focus on eye health and organ development.

Dr. Shailja Tibrewal is a Consultant in the Department of Pediatric Ophthalmology, Strabismus, and Neuro-ophthalmology at Dr. Shroff's Charity Eye Hospital (SCEH), New Delhi, where she has been working since 2013. She also heads the hospital's Ocular Genetics Clinic, which she established in 2018 to address the rising need for diagnosis and counseling of children with rare and inherited eye conditions.

Dr. Tibrewal earned her MBBS from Grant Medical College, Mumbai, and completed her MS in Ophthalmology from SMS Medical College, Jaipur. She further pursued a clinical fellowship in Pediatric Ophthalmology, Strabismus, and Neuro-ophthalmology at L.V. Prasad Eye Institute, Hyderabad—one of the most reputed institutes in India. She was selected for a prestigious

short-term NEI-sponsored training in Human Genetics and Genomics at the National Institutes of Health (NIH), Bethesda, USA.

Her primary research interests include complex strabismus, pediatric ocular genetic disorders, MAC (microphthalmia, anophthalmia, coloboma), myopia, and pediatric cataract. She has authored over 50 peer-reviewed publications in national and international journals.

Dr. Tibrewal has been the recipient of multiple accolades: the ARVO Developing Country Eye Researcher Fellowship (2020), a USAID grant (2022–2023) for pediatric eye screening in underserved communities of Delhi, and the Indo-US collaborative grant (2023) for research on MAC disorders and the retinoic acid pathway. In 2024, she became Co-Principal Investigator for the Velux Stiftung grant to establish the Center for Unknown and Rare Eye Disorders at SCEH.

Currently, she serves as the Secretary General of the Global Eye Genetics Consortium (GEGC) and plays an active role in mentoring the next generation of ophthalmologists, including fellows and DNB residents at SCEH.

Answers to Trivia

1. B
2. A
3. C
4. D

Figures are from internet

Ophthalmic Genetics News

Around the World

Primary endpoint not achieved in LUMEOS Phase 3 trial for treatment of XLRP

In the LUMEOS Phase 3 clinical trial, a gene therapy designed to treat X-linked retinitis pigmentosa (XLRP) caused by mutations in the gene RPGR did not achieve its primary goal of improving patients' ability to navigate visually. XLRP is a rare, inherited retinal disorder that primarily affects males and typically begins in childhood. Women are usually unaffected carriers but can also be affected. The therapy, known as botaretigene sparoparvovec (bota-vec), is an experimental treatment that delivers a functional RPGR gene to the retina via an adeno-associated virus. Johnson acquired full rights to this therapy in 2023 through a deal with MeiraGTx. The trial, being one of the few late-stage trials targeting this rare, progressive genetic eye disease, involved 95 participants, 58 of whom received either a low or high single dose of bota-vec. All patients treated in LUMEOS had at least one treatment- emergent event, most of which were mild or moderate.

Unfortunately, the treatment did not meet its main efficacy endpoint—enhancing vision-guided mobility within a virtual maze i.e performance in navigation of a maze under reduced illumination. All participants experienced at least one adverse event following treatment, with 86% classified as mild or moderate. Notably, over half (53%) had at least one side effect directly related to bota-vec. While the therapy didn't meet its primary benchmark, some statistically significant improvements were observed in secondary measures. In fact, 22 of the 55 treated patients showed positive changes in at least two endpoints—compared to none in the control group. Some patients also had improvements in low-luminance visual acuity (LLVA), which is their ability to read an eye chart in reduced light, and static perimetry, which measures retinal sensitivity at different locations (loci) in the retina. As of April 25, 2025, Johnson continued to monitor patients in a follow-up Phase 3 study. Although the findings indicate therapy might be showing some beneficial effects, gaining regulatory approval will likely be challenging due to the failure to meet the primary endpoint. Despite this, a spokesperson noted that the company is analyzing the broader dataset, including encouraging signs from several secondary endpoints, as it considers its next strategic steps.

Sources:

1) Ophthalmology Times. J & J gene therapy treatment fails primary endpoint. Accessed June 19, 2025.https://www.ophthalmologytimes.com/view/j-j-gene therapy-treatment-fails-primary-endpoint.

2) Incorvaia D. J&J gene therapy fails to improve visual navigation in late-stage rare eye disease trial. Fierce Biotech. Published May 5, 2025. Accessed May 15, 2025. https://www.fiercebiotech.com/biotech/jj-gene-therapy-fails-improve-visual navigation-late-stage-rare-eye-disease-trial

3) Armstrong A. MeiraGTx gifts remaining gene therapy rights to J&J for up to $415M. Fierce Biotech. Published December 21, 2023. Accessed May 15, 2025. https://www.fiercebiotech.com/biotech/meiragtx-gifts-remaining-gene-therapy- rights-jj-415m

4) Fighting Blindness Foundation. Accessed June 19,2025. https://www.fightingblindness.org/news/arvo -2025 -Highlight- J-J-s - XLRP- Gene- Therapy- Didn't-- Meet Primary- Endpoint- in -Phase- 3- Clinical - Trial —2290 Foundation Fighting Blindness.

New Genetic Mutations Linked to Inherited Retinal Disorders uncovered by University of Oklahoma researchers

A recent study by Lea D. Bennett, PhD and her team from the Dean McGee Eye Institute at the University of Oklahoma has identified 20 previously unknown gene mutations linked to rare inherited retinal diseases (IRDs). The research, with testing supported by the Foundation Fighting Blindness, a Maryland-based non-profit, aims to enhance diagnostic precision and pave the way for targeted therapies. Inherited retinal diseases are a group of rare vision-threatening conditions that damage the retina—the eye's light-sensitive tissue. Affecting roughly 1 in 3,000 people, these disorders have been linked to 326 of the approximately 20,000 human genes. Yet, a portion of patients diagnosed with IRDs show no detectable genetic mutations, a gap Dr. Bennett's team set out to investigate. At present, Luxturna remains the only FDA-approved gene therapy for IRDs. These investigators conducted a genetic analysis of 103 unrelated individuals with IRDs. Mutations were found in 70 cases, including 20 novel variants associated with conditions such as retinitis pigmentosa, cone-rod dystrophy, macular diseases, and third-branch retinal disorders. The gene ABCA4 emerged as the most commonly mutated. New mutations were also discovered in ALMS1, GNAT1, RAX2, and RDH5. However, 33 participants had no identifiable genetic mutations. Dr. Bennett suggests that undiagnosed late-onset IRDs or yet-to-be-discovered genetic links may explain these cases—underscoring the need for continued research.

According to Dr Bennett,
"These findings help confirm clinical diagnoses, support patient counseling around prognosis and family planning, and inform treatment strategies. Beyond offering hope to affected individuals, this work broadens our understanding of the genetic landscape of IRDs. We still have much to learn about hereditary retinal diseases. Mapping the underlying genetic mutations is the critical first step toward developing effective treatments". The team hopes their findings will accelerate the search for additional therapies for IRDs and assist pharmaceutical developers in identifying suitable candidates for clinical trials.

Sources:
Eyewire. University of Oklahoma study identifies 20 novel variants for inherited retinal diseases. Accessed June 19,2025.https://eyewire.news/news/university-of-oklahoma-study-identifies-20-novel-variants-for-inherited-retinal diseases?c4src=article: infiniti-scroll