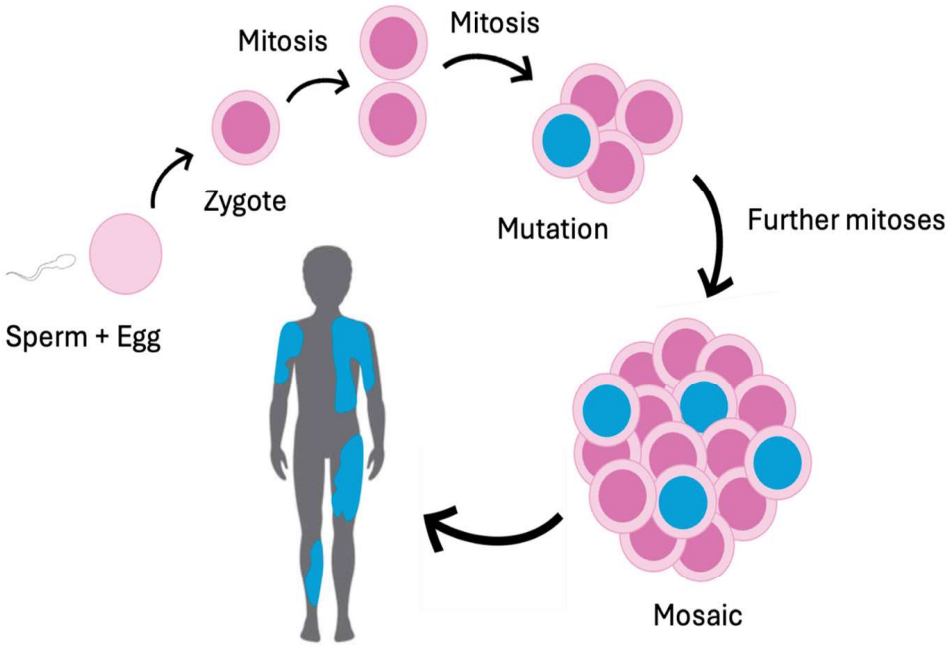
Global Eye Genetics Consortium

Newsletter #12

Genetics 101 | Genetic Mosaicism

Mosaicism: A Key Concept in Human Genetics



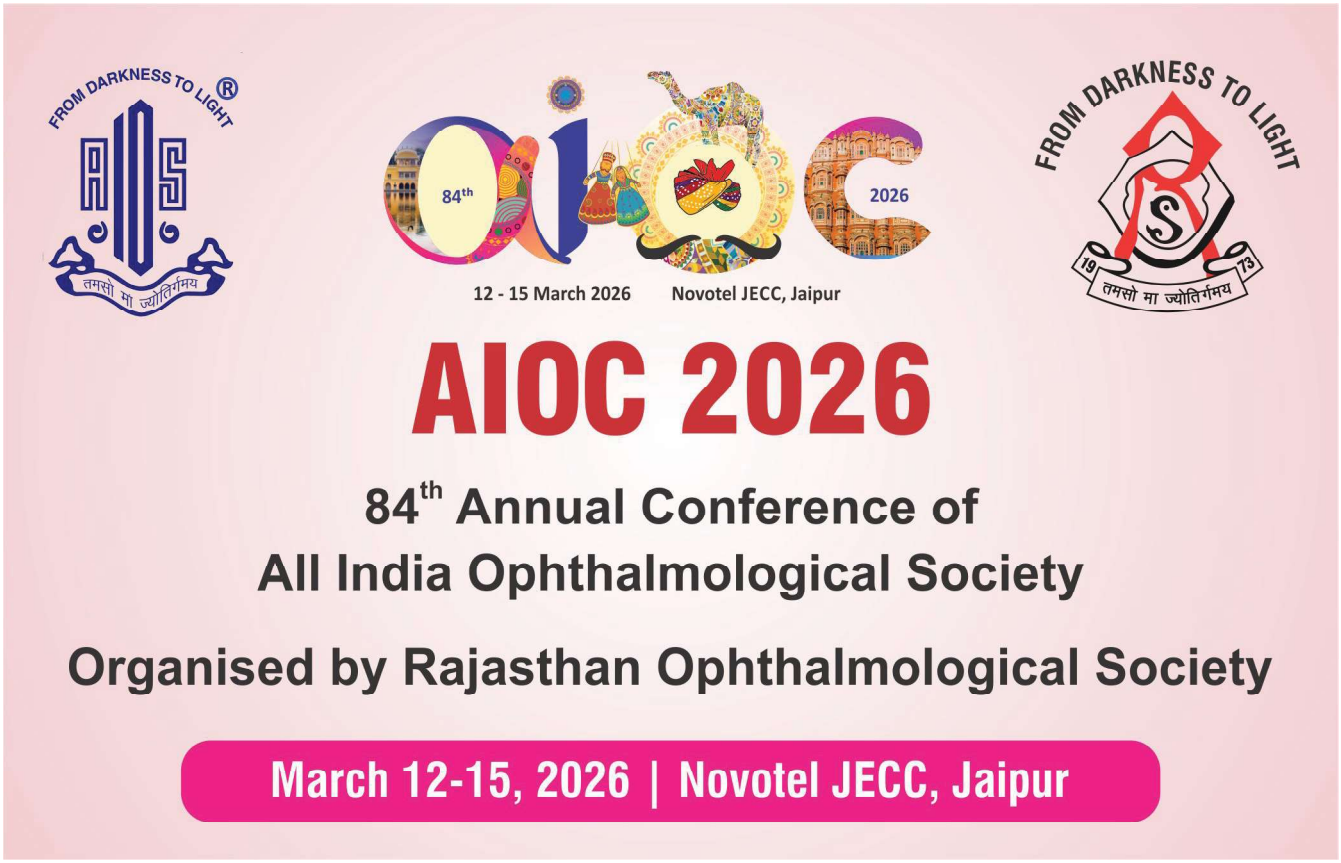
Reference: Geiger H, Furuta Y, van Wyk S, Phillips JA III, Tinker RJ. The Clinical Spectrum of Mosaic Genetic Disease. Genes. 2024;15(10):1240. doi:10.3390/genes15101240.

Genetic mosaicism refers to the presence of two or more genetically distinct cell populations within a single individual, arising from mutations that occur at different stages of development. When a genetic change occurs **before zygote formation** (i.e., in parental germ cells), it is transmitted to all cells of the offspring and follows classical inheritance patterns. In contrast, mutations that arise **after zygote formation** lead to mosaicism, with only a subset of cells carrying the genetic alteration. The timing of the post-zygotic event determines the proportion and distribution of affected cells across tissues.

The clinical presentation and recurrence risk in mosaic conditions depend largely on **which tissues harbour the mutant cells.** If mosaicism is confined to somatic tissues, the condition affects only the individual and is typically not inherited. However, if the mutation is present in the **germ cells** as well as **somatic cells (Germline mosaicism)**, there is a risk of transmission to offspring, even if the parent is clinically unaffected. Sometimes, the mutation arises in the germ cells, i.e, the sperm and the egg cells and will be confined to gonadal tissue. This type of mosaicism is called **Gonadal mosaicism**. This distinction is critical for genetic counselling, as recurrence risk cannot always be predicted based solely on parental phenotype or standard blood-based genetic testing. A well-recognized example of gonadal mosaicism in ophthalmology is **retinoblastoma**. Parental gonadal mosaicism can result in offspring developing bilateral heritable retinoblastoma, even when the parent is clinically unaffected and genetic testing of the parent's blood sample fails to detect the pathogenic variant.

A classic example of somatic mosaicism is S**turge–Weber syndrome**, caused by a post-zygotic activating mutation in the *GNAQ* gene. The mutation occurs early in embryonic development and affects only certain cell lineages, leading to characteristic facial capillary malformations, leptomeningeal involvement, and ocular features such as glaucoma. Because the mutation is not present in germ cells, Sturge–Weber syndrome is typically sporadic and not inherited, illustrating how mosaicism explains localized disease without familial transmission.

Upcoming Sessions of GEGC in Gobal Forums



TRIVIA

Rearrange the jumbled letters to guess the famous Scientific personality

- **Deward Mautt:** "One gene–one enzyme" hypothesis
- **Rah Bodign Krahona**: Genetic code and protein synthesis
- **Rederfick Garsen:** Recombinant DNA and DNA sequencing
- **Sejoph Rymaru:** Transplant biology (histocompatibility)
- **Erjinnef Dunado:** CRISPR-Cas9 genome editing
- **Wred Sewsaimn:** mRNA modification enabling mRNA therapeutics (genetic engineering relevance)
- **Ryka Lusmil:** PCR & site-directed mutagenesis.

Ophthalmic Genetics News

Around the World

SKYLINE trial suggests gene therapy may improve retinal performance in X-linked RP.

At EURETINA 2025 in France, it was announced that, in a clinical trial funded by Beacon Therapeutics, a gene therapy targeting X-linked retinitis pigmentosa-a degenerative disease caused by mutations in the RPGR gene-showed signs of improving retinal function for up to three years after treatment. According to Paul Yang, MD, PhD, Chief of the Genetics Division at Oregon Health and Science University in Portland, Oregon, the phase 2 SKYLINE trial of the gene therapy lura-zova (laruparetigene zovaparvovec) showed that the high-dose treatment produced sustained improvement in retinal sensitivity through month 36.

The trial enrolled 14 males aged between 8 and 50 years with the disease. With the vectors being surgically placed under the retina, eight patients were in the high-dose group who received 680 billion vector genes per eye, and six were in the low-dose group, who received a dose of 75 billion vector genes per eye. The measure of efficacy for the treatment was a more than 7-decibel improvement from baseline in more than five loci, or positions, in the chromosome: with a decibel being the measure of retinal sensitivity to light. Retinal sensitivity was measured using microperimetry. Yang discussed why the primary efficacy target was chosen, noting that the 7-decibel/five-loci standard is debated. According to Yang, Biogen's phase 2/3 RPGR gene therapy did not achieve this benchmark, and many experts believe it sets the bar too high. He added that sponsors are hesitant to use microperimetry as a key endpoint again because the FDA insists on the 7-decibel/five-loci requirement. Yang also mentioned the unsuccessful phase 2/3 XIRIUS trial of cotoretigene toliparvovec for treating X-linked retinitis pigmentosa.

At 3 years, four of seven eyes in the high-dose group (57%) met that standard, whereas none of the fellow, untreated eyes in these patients did so. Patients in the SKYLINE trial tolerated the treatment well and had an acceptable level of adverse events, he added. Those in the low-dose group experienced two ocular adverse events — one case each of glaucoma and visual impairment — and six treatment-related adverse events. Patients in the high-dose group experienced two cases of vitritis, which resolved in 4 months with corticosteroids treatment, Yang said. No adverse events were reported in the fellow, untreated eyes. Yang noted that the findings to date support advancing the high-dose regimen into phase 3 trials. "These results are promising for a gene-augmentation approach aimed at one of the most common types of retinitis pigmentosa," said Neiraj Jain, MD, a retina specialist at Emory University in Atlanta. "The longer-term data suggest a sustained treatment effect with an acceptable safety profile, supporting further development." He pointed out that some 36-month SKYLINE data were missing for several eyes, and that some control-group eyes left the study because they later received treatment in a related trial. "It would be helpful to review the most recent functional assessments for those eyes," he said. He added that the SKYLINE trial did not evaluate low-luminance visual acuity(the primary outcome for the pivotal phase 2/3 VISTA study now underway), which evaluates cone

function and reading ability in dim lighting . According to Yang, 12-month outcomes from the phase 2/3 VISTA trial of lura-zova should be available within the next 12 months. He added that follow-up for the SKYLINE study will continue for up to five years.

Sources consulted:
1) Gene Therapy Shows Signal for Improving Retinal Function - Medscape - September 19, 2025
(https://www.medscape.com/viewarticle/gene-therapy-shows-signal-improving-retinal-function-2025a1000owk)
2) Beacon Therapeutics Announces Positive Interim 9+ Month Results from DAWN Trial and 36-Month Phase 2 SKYLINE Trial Data for Laru-zova in Patients with X-linked Retinitis Pigmentosa (XLRP) at EURETINA 2025 - Beacon Therapeutics. Beacon Therapeutics. Published September 4, 2025. Accessed September 8, 2025.
https://www.beacontx.com/news-and-events/beacon-therapeutics-announces-positive-interim-9-month-results-fromdawn-trial-and-36-month-phase-2-skyline-trial-data-for-laru-zova-in-patients/

A Mutation-Agnostic Optogenetic Strategy (MCO-010) for Vision Recovery in Retinitis Pigmentosa

A new optogenetic gene therapy, MCO-010, may help people with advanced retinitis pigmentosa (RP) regain functional vision, regardless of which gene mutation caused their disease. Unlike mutation-specific therapies, MCO-010 works by genetically programming retinal bipolar cells to produce a light-sensitive protein, potentially restoring visual responses even when photoreceptors are lost.

The only FDA-approved gene therapy for RP, Luxturna, treats patients with mutations in both copies of RPE65, a group that represents fewer than 2% of RP cases. As reported in September 2025, researchers discussed 3-year follow-up data from patients who received MCO-010 in a phase 2b trial in separate presentations at the EURETINA 2025 Congress and at the annual scientific meeting of The Retina Society. Samarendra Mohanty, PhD, the president and chief scientific officer of Nanoscope Therapeutics, the company developing MCO-010, also described the treatment during a virtual meeting in September held by the FDA's Center for Biologics Evaluation and Research about facilitating the development of cell and gene therapies. No serious adverse events or safety concerns had been reported in the clinical trials of MCO-010.Nanoscope Therapeutics has begun the Biologics License Application process, aiming for full FDA submission in early 2026. Delivered as a single intravitreal injection, the therapy uses AAV2 to introduce a synthetic multi-characteristic opsin gene into retinal cells. Early open-label studies in blind patients demonstrated improvements in visual function and mobility. In the RESTORE phase 2b trial, patients receiving either low or high doses showed significant improvements in best-corrected visual acuity at 52 weeks compared with controls. These gains persisted over nearly three years, indicating durable benefit and good long-term tolerability.

MCO-010 is being investigated by Nanoscope for other retinal diseases, including Stargardt disease, geographic atrophy, and Leber congenital amaurosis. European regulators are also reviewing it for various rod- and cone-related dystrophies. Several other mutation-agnostic gene therapy approaches—such as Ocugen's OCU400, Ray Therapeutics' RTx-015,Restore Vision's RV-001, and AbbVie's RST-001—are also in development. Unlike some optogenetic systems requiring special goggles, MCO-010 works without external devices.

Sources consulted:
1) Mutation-Agnostic Gene Therapy May Restore Vision in RP - Medscape - October 02, 2025.
https://www.medscape.com/viewarticle/mutation-agnostic-gene-therapy-may-restore-vision-rp-2025a1000qir
2) Nanoscope Announces Groundbreaking 3-year REMAIN Trial Data for Patients with Retinitis Pigmentosa at 2025 Euretina Congress and Retina Society Annual Scientific Meeting. Nanoscope Press Release.
https://nanostherapeutics.com/2025/08/26/nanoscope-announces-groundbreaking-3-year-remain-trial-data-for-patients-with-retinitis-pigmentosa-at-2025-euretina-congress-and-retina

KNOW OUR MEMBERS

Ms. Ria Sachdeva is an accomplished Genetic Counselor specializing in human molecular genetics, ocular genetics, and the molecular study of retinoblastoma. She has been serving as a Genetic Counselor at Dr. Shroff's Charity Eye Hospital, New Delhi since October 2018.

Ria holds an M.Sc. in Human Molecular Genetics from Imperial College London and a B.Sc. (Hons.) in Genetics from the University of Liverpool. She is a certified Level II Genetic Counselor from the Indian Board of Genetic Counseling and is currently pursuing PhD at Manipal Academy of Higher Education. She also completed a certificate course in Genetic Counseling from Manipal Hospitals, Bengaluru.

Her research focuses on rare and inherited eye disorders, and she has been recognized as co-PI on international grants including the U.S.-India Collaborative Vision Research Grant (2025–2028) and the Velux Stiftung Grant for establishing the Centre for Rare and Unknown Eye Disorders (CURED) in India (2025–2029). She also received the SERB ANRF grant for organizing the CONCURED 2024 conference and multiple international travel fellowships for ARVO 2025 and ISOO 2024.

Ria has contributed extensively to the field through numerous peer-reviewed publications, including studies on retinoblastoma, aniridia, congenital glaucoma, and hereditary optic neuropathies. She has delivered invited talks and lectures at national and international conferences, including ARVO, APAO-AIOS 2025, and the National Genetic Counseling Symposium 2025, and has presented multiple posters on ocular genetics.

Her work has been recognized with awards such as the Best e-Poster at ISOO 2024 and the Rare Star Award 2025. Ria has completed observerships at Memorial Sloan Kettering Cancer Center (USA), Bascom Palmer Eye Institute (USA), and Guy's Hospital (UK).

Ria serves as a member of the Centre for Unknown and Rare Eye/ENT Disorders (CURED) and the Global Eye Genetics Consortium (GEGC), where she is also an editor for their newsletter. She actively participates in organizing workshops, conferences, and educational programs in ocular genetics, contributing to advancing patient care and research in rare eye disorders.

Dr. Shiva Ram Male is an Assistant Professor at the School of Medical Sciences, University of Hyderabad, before joining UoH Dr. Shiva worked as Postdoctoral Research Fellow at the Schepens Eye Research Institute, Harvard Medical School, Boston, USA . He is an emerging interdisciplinary scholar whose work bridges vision science, culture, and the deeper perceptual narratives that shape human experience. Grounded in visual psychophysics and advanced vision science, his research examines how colour, perception, and cultural frameworks interact to influence the ways individuals see, understand, and interpret their world.

Currently His scholarly contributions span a wide and distinctive spectrum, including cognition, colour–emotion associations, retinal forensics, language phylogenetics, Color vision genetics,neuro-

degenerative diseases and public health strategies designed to meet global challenges through context-sensitive, locally grounded solutions. He is editorial board for PLOS-ONE journal andRe-search coordinator for (India Cohort) -IC&SR - IIT Madras Davos Alzheimer's Collaborative -initiative of World Economic Forum working towards Alzheimer's research.His research work is published in top American and international prestigious journals and presented work at ARVO,VSS, ECVP and CogSci conferences.

Dr. Ogugua Ndubuisi Okonkwo is a distinguished ophthalmologist recognized for his expertise in retinal diseases and their management. With extensive clinical experience at the Eye Foundation Retina Institute and Eye Foundation Hospital in Nigeria, he has established himself as a leading authority in the diagnosis and treatment of complex retinal conditions, including retinal detachment, proliferative sickle cell retinopathy, and age-related macular degeneration.

Dr. Okonkwo's research contributions continue to elevate the understanding of retinal health in Sub-Saharan Africa. His recent publications explore critical topics such as retinal detachment and treatment outcomes in low-resource settings, the prevalence of retinal vascular occlusions, and the application of optical coherence tomography in lower-middle-income settings. His work not only addresses pressing regional challenges but also adds valuable insights to global ophthalmic research.

His dedication to advancing clinical and scientific excellence is further reflected in the support he has received toward establishing a pan-African research network that will provide valuable insights into the burden and outcomes of various retinal diseases. Through collaborations with academic and research institutions, Dr. Okonkwo actively contributes to innovations that improve patient outcomes and strengthen retinal care services.

Committed to preventing blindness and enhancing visual health, Dr. Okonkwo's work continues to make a meaningful impact both within Nigeria and across the broader ophthalmology community. His blend of clinical expertise, academic engagement, and research leadership highlights him as a transformative figure in modern retinal medicine.

Professor Raj Ramesar is an internationally recognized leader in the field of human genetics, renowned for his pivotal role in advancing research that specifically addresses the unique health challenges of South African populations. Professor Ramesar has dedicated his distinguished career to the University of Cape Town (UCT), where he has been an influential figure for decades. He served as the Head of the Division of Human Genetics at UCT for the past 25 years. He is currently the Director of the Medical Research Council (MRC) Genomic and Precision Medicine Research Unit, located within the Institute of Infectious Diseases and Molecular Medicine at UCT.

Professor Ramesar's research has been consistently at the forefront of identifying the genetic factors underlying diseases prevalent in South Africa. His work is highly translational, successfully bridging laboratory discoveries with clinical insights for public benefit. He is the principal investigator on the long-standing Retinal Degenerative Disorders research project, which, in collaboration

with Retina South Africa, has established a vital registry and database. His team's efforts have been crucial in identifying the genetic basis of inherited retinal diseases and familial cancers, particularly colorectal cancers.

His groundbreaking work has led to the establishment of comprehensive services for genetic testing and genetic counselling in South Africa, including the appropriate vocational training programs. This infrastructure facilitates confirmatory and predictive genetic testing, as well as essential cascade screening in affected families and communities.

In recent years, his research portfolio has broadened to include complex and widely prevalent chronic diseases such as cardiovascular diseases and neuropsychiatric conditions (e.g., Genomics of Psychiatric Disorders project). By unravelling the interplay of genetic and environmental influences in these high-burden conditions, his work aims to translate findings into meaningful clinical insights for diverse communities.

Professor Ramesar's contributions have earned him significant local and international accolades. He received the prestigious Human Genome Organisation's (HUGO) Africa Award in 2016 for his role in advancing genomic medicine on the continent. He was awarded the UCT Vice Chancellor's Alan Pifer Award for outstanding research in cancer genetics that demonstrates relevance to the advancement of South Africa's disadvantaged populations. He has also been elected to the College of Fellows of the University of Cape Town.

Professor Ramesar is a dedicated educator and a key figure in building genetic research capacity across Africa and globally. He has authored more than 300 scientific works and serves on the editorial board of a number of international peer-reviewed journals. He has designed genetic/genomic modules for various levels of postgraduate training, including clinical specialties, and has supervised numerous PhD students. He serves as the Head of Education and Training in the Global Eye Genetics Consortium, further extending his impact on genetic research and capacity-building at an international level. He is currently the Co-chair of the Scientific and Medical Advisory Board of Retina South Africa and serves on the Executive Committee (as Traesurer) of the African Society for Human Genetics.

Professor Ramesar's leadership has been instrumental in establishing collaborative research platforms, fostering ethical research practices, and strengthening the infrastructure for genomic medicine in Africa. Beyond his academic work, he holds an Executive MBA and has non-academic pursuits including bonsai and painting in watercolours.

Answers to Trivia

- **Edward Tatum**
- **Har Gobind Khorana**
- **Frederick Sanger**
- **Joseph Murray**
- **Jennifer Doudna (Chemistry)**
- **Drew Weissman**
- **Kary Mullis**

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