## Commentary: Genomic testing is a powerful tool in diagnosing and managing anterior segment dysgenesis

Genomic testing may provide individuals and families with information on the nature, mode of inheritance, and how test results may help them make informed medical and personal decisions. This commentary provides the clinician's perspective with genetic risk assessment, family history, and genetic testing to clarify the genetic status of family members. It is not meant to address all personal, cultural, or ethical issues that may arise or substitute for consultation with a genetics professional.[1]

Anterior segment dysgeneses (ASD) encompasses a broad spectrum of developmental abnormalities that contributes to a substantial burden of childhood corneal blindness in many consanguineous populations worldwide, including India. ASD affects multiple anatomical structures of the eye, including the cornea, iris, sclera, ciliary body and aqueous outflow pathways, exhibiting different phenotypes with overlapping clinical features in the disease spectrum.[2] The pathogenesis of ASD is multifactorial and includes sporadic, environmental, and genetic factors or is related to intrauterine infections. ASD demonstrates different modes of inheritance and a high degree of inter- and intra-familial phenotypic variability. Therefore, the patient receiving a molecular diagnosis has a distinct advantage: an end to the diagnostic odyssey, determination of prognosis and clarification of treatment, access to proper genetic counseling, and confirming eligibility for clinical trials or genetic-specific therapies.[1–3]

A review by Arif *et al*.[4] provides the rationale for genetic testing in ASD. The review discusses the benefits of precise diagnosis by genomic methods in anterior segment disorders, which helps in providing accurate prognosis, assists in genetic counseling and prenatal diagnosis, and helps patients to participate in potential gene-specific therapeutic trials. Prerequisites for a successful outcome of a genomic screening are an accurate clinical diagnosis, a careful family pedigree that guides focused genetic testing, and genetic counseling (both pre-test and post-test). Therefore, it is crucial to classify phenotypes accurately based on anterior segment features, and these findings should be corroborated using an appropriate anterior segment imaging that helps determine valid genotype–phenotype correlations accurately.[2]

Recent advancement in molecular biology and genomics, and its application in translational health science has enabled the

discovery of genes and mutations involved in ASD. Genomic testing assesses many genes in one test. It is often used to diagnose heterogeneous single gene disorders where pathogenic variation in one of many genes is known to cause similar phenotypes or where a clinical diagnosis is difficult to reach. Genomic testing can diagnose several diseases in the ophthalmic setting, including inherited retinal dystrophies, pediatric cataracts, glaucoma, anterior segment dysgenesis, and other syndromic developmental disorders with eye involvement. The testing can encompass several modalities ranging from whole-genome sequencing to exome sequencing or targeted gene panels. The advantages to the patient of receiving a molecular diagnosis include an end to the diagnostic odyssey, determination of prognosis and clarification of treatment, access to proper genetic counseling, and confirming eligibility for clinical trials or genetic-specific therapies. Genomic testing is a powerful addition to diagnosing and managing inherited eye disease.[2–5]

A protocol for genetic testing is presented. If specific mutations in a gene are common, they should be the first-tier test, such as the mutations in PAX6. If mutations in one gene are likely, sequencing of that gene should be carried out; for example, genes like PAX6 in Aniridia, PITX2, FOXC1 in Axenfeld-Rieger Syndrome, PAX6, PITX2, CYP1B1, FOXC, B3GALTL in Peters anomaly, and FOXE3 in congenital primary aphakia. Such an approach is helpful for their characterization of the genotype. On the other hand, the disorders with genetic heterogeneity require multi-gene panel tests, and if these tests show no abnormality, then deletion or duplication or microarray studies are recommended, followed in sequence by clinical exome sequencing (5000 to 6000 genes), whole-exome sequencing (about 20,000 genes, or whole-genome studies (includes all introns). Despite numerous advances, phenotypic and genotypic heterogeneity pose continuing challenges to understand the mechanisms underlying the complexity of ASD. Genomic methods, such as genome-wide association studies, are potentially an effective tool to understand anterior segment dysgenesis and the individual's susceptibility to the development of ASD.[2-6]

Molecular cell biology and genetic analyses of congenital eye diseases have provided important information on the regulation of neural crest cells (NCCs) that play an important role in the development of the anterior segment of the eye. Nevertheless, a complete understanding of the NCC as a contributor to ocular development remains elusive. In addition, positional information during ocular NCC migration and the molecular pathways that regulate end tissue differentiation have yet to be fully elucidated. Furthermore, the clinical challenges of ocular diseases, such as Axenfeld-Rieger syndrome (ARS), Peters anomaly (PA), and primary congenital glaucoma (PCG), strongly suggest the need for better treatment. While several aspects of NCC evolution have recently been reviewed, this discussion will consolidate the most recent knowledge on the contributions of the NC in ocular development, especially the anterior segment, and the knowledge obtained from its clinical manifestations associated with diseases. This knowledge can ultimately inform translational discoveries with the potential for regenerative therapies.[7] Therefore, for an ophthalmologist, genetic testing should be as focused and ordered based on the specific phenotype and if testing will answer specific questions. Testing should be done by understanding its importance and limitations, and interpretation of analysis should be made along with a trained individual, such as a medical geneticist and a genetic counselor within ophthalmic and pediatric clinics are likely to improve the delivery of clinical care in these settings.

***Muralidhar Ramappa[1,2,3], Anshuman Verma[4], Deepak P Edward[5]***

[1]Institute for Rare Eye Diseases and Ocular Genetics, L V Prasad Eye Institute, [2]The Cornea Institute, L V Prasad Eye Institute, [3]Jasti V Ramanamma Children's Eye Care Center, L V Prasad Eye Institute, Hyderabad, India, [4]M R Medical College, Telangana, India, [5]University of Illinois Eye and Ear Infirmary, Chicago, IL, USA

Correspondence to: Muralidhar Ramappa, Head, Institute for Rare Eye Diseases and Ocular Genetics, Consultant, The Cornea Institute & Jasti V Ramanamma Children's Eye Care Center, L V Prasad Eye Institute, Hyderabad, Telangana, India.
E-mail: muralidhar@lvpei.org.

## References

1. Abu-Amero KK, Edward DP. Primary Congenital Glaucoma. In: Adam MP, Mirzaa GM, Pagon RA, *et al*., eds. GeneReviews®. Seattle (WA): University of Washington, Seattle; September 30, 2004.
2. Nischal KK. Genetics of congenital corneal opacification--impact on diagnosis and treatment. Cornea 2015;34(Suppl 10):S24-34.
3. Reis LM, Semina EV. Genetics of anterior segment dysgenesis disorders. Curr Opin Ophthalmol 2011;22:314-24.
4. Kaushik S, Dubey S, Choudhary S, Ratna R, Pandav SS, Khan AO. Anterior segment dysgenesis: Insights into the genetics and pathogenesis. Indian J Ophthalmol 2022;70:2293-303.
5. Burdon KP. The utility of genomic testing in the ophthalmology clinic: A review. Clin Exp Ophthalmol 2021;49:615-25.
6. Scanga HL, Nischal KK. Genetics and ocular disorders: A focused review. Pediatr Clin North Am 2014;61:555-65.
7. Williams AL, Bohnsack BL. The ocular neural crest: Specification, migration, and then what? Front Cell Dev Biol 2020;8:595896. doi: 10.3389/fcell.2020.595896.



**Access this article online**

Quick Response Code:

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_1022_22

**Cite this article as:** Ramappa M, Verma A, Edward DP. Commentary: Genomic testing is a powerful tool in diagnosing and managing anterior segment dysgenesis. Indian J Ophthalmol 2022;70:2303-4.