

Unlocking the Genetic Mysteries of Eye Diseases: Empowering Patients and Transforming Care

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Disclaimer: The author has no financial disclosures.

Imagine a couple's desire to bring a child into the world, only to be burdened by uncertainty. Their hopes waver as the male partner's mother has been diagnosed with retinitis pigmentosa (RP), a potentially blinding eye condition. Will their offspring inherit the condition, even if the male partner shows no symptoms?

In another compelling case, a 17-year-old boy seeks medical attention for blurred vision. Little did he know that his eyes were windows to a deeper issue. An ophthalmologic examination uncovers signs of RP, but that's not all. The young patient also has type 1 diabetes mellitus, hypogonadism, polydactyly, and truncal obesity. Are these systemic findings related to his eye condition?

Then, there is the case of a 2-year-old child with blurred vision and nystagmus. The examination reveals remnants of the iris and macular hypoplasia in both eyes. What could possibly be causing such a condition? And is this child at risk of a life-threatening situation?

Enter the subspecialty of ocular genetics, which seeks to answer these questions and unravel the mysteries of genetic eye diseases (GEDs). Ocular genetics delves into the realm of gene-based testing and treatments, forging collaborations among clinical and molecular geneticists, genetic counselors, and other medical specialists to ensure holistic patient care.

Unraveling the genetic code

Advancements in the field of genetics have revolutionized our understanding of GEDs. From the discovery of the deoxyribonucleic acid (DNA) in 1896 to the groundbreaking development of the first vision-restoring gene therapy for an inherited retinal disease called Leber congenital amaurosis in 2017, we have come a long way.¹ The expansion of genetic knowledge has granted us the ability to comprehend GEDs at a molecular level through genetic testing. A genetic diagnosis provides a vital opportunity to offer patients precise disease prognosis, insights into transmission to future generations, potential gene-based treatment options, and appropriate referrals to medical specialists. Moreover, it deepens our understanding of the mechanisms underlying these diseases, as we correlate the affected gene's function with the clinical manifestations.

A Vast Genetic Landscape

Over 400 genes have been found to be associated with various GEDs, affecting both the anterior and posterior segments of the eye.² Some of these disorders include strabismus, keratoconus, corneal dystrophy, Axenfeld-Rieger anomaly, aniridia, congenital glaucoma, and congenital cataract. On the other hand, the posterior segment disorders include RP, Stargardt disease, X-linked juvenile retinoschisis, and hereditary optic

neuropathy, among others. These GEDs can occur in isolation or as part of a syndrome. Each of these conditions arises from specific genetic abnormalities, highlighting the intricate nature of ocular genetics and its role in shaping the development and function of the eye's structures. Each genetic discovery propels us further in understanding the complex interplay between genes and vision.

The Path to Diagnosis

The journey to understanding and managing GEDs is a meticulous process. It begins with identifying a patient's phenotype, the observable characteristics, through history-taking and the creation of a detailed family pedigree. This is followed by comprehensive ocular examinations, aided by the appropriate diagnostic tools, and an in-depth review of the patient's systemic health. Once the phenotype is established, a specific genetic test is selected. Genetic counseling is an indispensable step that precedes and follows genetic testing, allowing patients and their families to comprehend the risks and benefits involved.

Genetic testing itself involves submitting a patient specimen (i.e., saliva or blood) to a certified laboratory, where the appropriate test is conducted. The various genetic tests range from karyotyping, which captures a "picture" of the chromosomes to identify aberrations, to chromosomal microarray, capable of detecting smaller affected segments, and even next-generation sequencing, which enables a comprehensive "reading" of nucleotide sequences to identify specific genetic mutations associated with the disease.

Analysis of a genetic test result is a crucial step in the process of diagnosing GEDs, as the result may be reported as "positive", "negative", or "uncertain". The interpretation of test results involves careful examination and validation of the findings which includes reviewing literature, accessing genetic databases, and further examination of family members. Once the results are thoroughly reviewed and understood, genetic counseling plays a vital role to explain the implications of the test results, the specific genetic eye disease, and its inheritance pattern. Genetic counseling aims to help patients and their families comprehend the condition, its potential impact on their health, and the available management options.

Decoding Lives

Let's revisit the cases that we previously discussed. In the first case, the male patient was identified as a carrier of a mutation in the *CERKL* gene associated with autosomal recessive RP. This gene plays a role in providing protection to cells under conditions of oxidative stress. Since the patient had only one copy of the mutation, he remained asymptomatic. However, the mother had both copies affected, resulting in the manifestation of the disease.

The couple, after understanding the small risk involved, made an informed decision to have a child. The likelihood of having an affected child in this case was determined to be only 1.5%. It is important to note that genetic counseling played a significant role in helping the couple understand the implications and risks associated with their specific genetic situation.

In the second case, the patient's ocular and systemic findings were linked to a mutation in *BBS10*, a gene associated with ciliary function, causing Bardet-Biedl syndrome. By facilitating referrals to appropriate subspecialties, we embraced a holistic approach to care. Through genetic testing, we identified both parents as carriers, informing them of the 25% chance of having another child with the same condition. Knowledge empowers families to make informed decisions, fostering resilience and support.

Lastly, in the case of the 2-year-old child with nystagmus, we discovered a mutation in *PAX6*, the master control gene of the eye. Through a comprehensive deletion analysis, we determined that the adjacent *WT1* gene associated with renal cancer was unaffected. Consequently, we eliminated the need for unnecessary renal screenings, allowing us to focus on early interventions for potential eye-related complications.

In addition to the previously mentioned genetic mutations, several other genes have been identified among Filipinos with GEDs. These include: *EFEMP1* causing juvenile open-angle glaucoma in three independent families, *BBS5* causing Bardet-Biedl syndrome in two female siblings,³ and *EYS*, *USH2A*, *CNGB1*, *SPP2*, *PDE6A*, *RPGR*, *FAM161A* and *FLVRC1* resulting in various inherited retinal diseases,⁴ both isolated and syndromic (T. Laddaran, personal communication, December 2022).

A Collaborative Future

Indeed, it is crucial to expand our understanding of GEDs and the specific mutations associated with them, particularly among the Filipino population. By gathering more comprehensive data on these genetic mutations, we can adopt a more streamlined approach to the diagnosis and management of GEDs, as well as ensure the availability of relevant resources.

Raising awareness among patients, family members, ophthalmologists, and other healthcare professionals is a vital step in this process. By educating and informing these stakeholders about the existence of genetic testing services for GEDs, we can promote early detection, accurate diagnoses, and appropriate management strategies. Establishing genetic databases within individual or institutional ophthalmology practices, which can potentially grow into a network of interconnected databases, will facilitate accessibility to genetic testing. This can be achieved through collaboration with private laboratories or participation in GED studies both locally and internationally.

The establishment of the Philippine Ocular Genetics Interest Group signifies a pivotal step forward. This group not only promotes awareness, medical education, and research about GEDs but also serves as a platform for collaboration. By pooling our collective knowledge and resources, we can enhance access to phenotypic profiling, genetic counseling, and genetic testing for Filipino patients. Through collaboration, we can break down barriers and foster a community dedicated to advancing ocular genetics.

The Promise of Gene-Based Treatments

While gene-based therapies are still in their infancy, their potential to revolutionize the treatment of GEDs is awe-inspiring. Clinical trials are already underway for other inherited retinal diseases such as X-linked RP, Usher syndrome, and Stargardt disease, among others, as well as for hereditary optic nerve disorders such as Leber hereditary optic neuropathy and autosomal dominant optic atrophy.

While GEDs may not be as common as other eye conditions, they are encountered in almost all ophthalmology subspecialty practices which present unique challenges and require specialized attention. As eye doctors, it is our responsibility to ensure that no patient is left behind. By empowering GED patients with knowledge about their condition and offering them opportunities for better disease management, we can pave the way for improved outcomes and potential participation in future advancements in genetic therapies.

Conclusion

As we witness the rapid progress in ocular genetics, it is essential that we seize this moment. By harnessing the power of genetic testing and collaboration, we can unlock the secrets behind genetic eye diseases and transform lives. Let us unite as a medical community, advocate for greater accessibility to genetic testing, promote genetic research, and raise awareness among patients and fellow healthcare professionals. No longer should patients feel helpless or left in the dark. Together, let us bring genetic eye disease out of the shadows and into the light of understanding, compassion, and hope.

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