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REPRODUCTIVE OPHTHALMOLOGY:

The Intersection of Inherited Eye Diseases and Reproductive Technologies

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Abstract

Purpose: To propose a working framework for patients with inherited eye diseases presenting to ophthalmologists who are interested in assisted reproductive technology and preimplantation genetic testing.

Methods: Retrospective chart review and case series of three families with inherited eye diseases who successfully underwent preimplantation genetic testing, in vitro fertilization, and birth of unaffected children.

Results: Preimplantation genetic testing was performed for three families with different inherited eye diseases, which included autosomal dominant retinitis pigmentosa, autosomal recessive achromatopsia, and X-linked Goltz syndrome. Preimplantation genetic testing led to the identification of unaffected embryos, which were then selected for in vitro fertilization and resulted in the birth of unaffected children.

Conclusion: A close collaboration between patients, families, ophthalmologists, reproductive genetic counselors, and reproductive endocrinology and infertility specialists is the ideal model for taking care of patients interested in preimplantation genetic testing for preventing the transmission of inherited eye diseases.

Keywords

assisted reproductive technologies; in vitro fertilization; inherited eye diseases; inherited retinal diseases; preimplantation genetic testing; reproductive endocrinology and infertility; reproductive ophthalmology

Inherited eye diseases (IED) are a heterogenous group of genetic conditions often associated with significant visual impairment.[1] All inheritance patterns are represented in IEDs, and the vast majority are caused by a single gene abnormality marked by extensive genetic and phenotypic heterogeneity.[2] Complex genetic phenomena that need to be accounted for

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when determining genetic causality include incomplete penetrance and variable expressivity resulting in nonlinearity between genotype and phenotype,[1] uniparental disomy[3] (where one receives two homologous chromosomes or chromosomal segments from one parent and no copy from the other parents), genetic mosaicism[4] (where one has at least two or more cell populations with distinct genotypes derived from a single fertilized egg), copy number variations[5] (where the number of copies of a gene may vary as a result of deletions, inversions, and duplications), and gene–environmental epigenetic changes including DNA methylation, histone modifications, chromatin remodeling, and noncoding RNA-associated gene regulations.[6]

A predominant type of IED is inherited retinal disease (IRD) with currently more than 260 causative genes identified and novel disease genes continuously being discovered.[7] For IRDs alone, panel-based genetic testing is able to identify the genetic cause of disease for approximately 67% of all patients with IRDs and up to 85% of children with IRDs.[7] As of 2020, roughly 5.5 million individuals (~1 in 1,380) are expected to be affected by an autosomal recessive (AR)-IRD, and 2.7 billion individuals worldwide (36% of the global population) are carriers of an IRD-causing mutation, a prevalence that is likely the highest across any group of human mendelian conditions.[8] One free option for IRD testing is through Invitae (San Francisco, CA) and Spark Therapeutics (Philadelphia, PA).

The current management of IEDs is limited. To date, there is only one FDA approved gene-based therapy of IEDs: voretigene neparvovec-ryzl (Luxturna)[9] for individuals with Leber congenital amaurosis and AR retinitis pigmentosa secondary to biallelic mutations in the *RPE65* gene. Luxturna for *RPE65*-mediated IRD, although revolutionary, comes with a cost of approximately $850,000 USD for both eyes.[10] Cost–benefit analyses examining Luxturna have yielded varying results likely because of variations in modeling methodology.[10]

Additional therapies being investigated for IEDs include gene augmentation and gene editing approaches for other mutations, optogenetics, cell-based therapies, retinal prosthetic devices,[11] and neuroprotective therapies such as N-acetylcysteine, ciliary neurotrophic factor, and rod-derived cone viability factor.[7,12] There are no current therapeutics approved in the United States for mitochondrial disease.

Reproductive technologies play a significant role in many other fields of medicine to help couples with family planning, fertility preservation, and fertility treatment in the setting of an inherited disorder. However, a formal approach toward the prevention of IEDs has not yet been standardized within the field of ophthalmology. Couples often initially approach reproductive endocrinology and infertility (REI) specialists after 1) experiencing difficulty with conception, 2) having a child diagnosed with an inherited genetic disease and inquiring about potential options for future unaffected children, and/or 3) having self-identified as affected by disease or as carrier(s) for an AR disease through genetic carrier screening panels, which are recommended for all individuals before or during pregnancy.

Those at risk of having a child with an inherited genetic disease have the option to undergo in vitro fertilization (IVF) with preimplantation genetic testing for aneuploidy (PGT-A) or preimplantation genetic testing for monogenic disorders (PGT-M, previously

known as preimplantation genetic diagnosis, or preimplantation genetic diagnosis (PGD)), to reduce the likelihood that their child is affected.[13,14] In vitro fertilization involves ovarian stimulation using exogenous gonadotropins such as follicle-stimulating hormone and luteinizing hormone to achieve multifollicular development, oocyte retrieval using ultrasound-guided transvaginal aspiration, and embryo creation through combining eggs and sperm in a dish or with intracytoplasmic sperm injection. The fertilized egg (embryo) is then cultured in vitro for two to six days until the embryo is transferred into the uterus using transabdominal ultrasound guidance. Commonly now-adays, the embryos are cultured for 5 days to 6 days, and at that developmental stage are called blastocysts. At this point, some couples may request genetic embryo testing, which requires embryo biopsy with subsequent embryo freezing and PGT-A or PGT-M procedures. Because of its high success rate in the recent years, IVF has been used very frequently, with approximately 2% of all babies in the US being born after IVF,[15] and preimplantation genetic testing (PGT) being used (as of 2018) in roughly 50% of all retrieval cycles.[16]

In this manuscript, we will review several case studies involving patients with IEDs that exemplify how assisted reproductive technologies (ART) can be harnessed to offer patients different options for managing their IEDs. This approach is not limited to these specific IEDs, but can be applied to most IEDs with causative, known genetic mutations. In doing so, we also provide a practical template about how ophthalmologists can collaborate with REI specialists to best serve patients who are interested in preimplantation genetic testing and reproductive planning for IEDs.

Methods

This study was a literature review and retrospective chart review conducted at Stanford University and adhered to the tenets of the Declaration of Helsinki. institutional review board (IRB)/Ethics Committee ruled that approval was not required for this study. Medical records of patients with IEDs identified through the Reproductive Endocrinology and Infertility clinic at Stanford and Lucile Packard Children’s Hospital were accessed in a Health Insurance Portability and Accountability Act (HIPPA) compliant fashion and reported with de-identified information. A literature review was conducted on PubMed for previous work conducted in the field of IEDs and reproductive medicine in collaboration with ophthalmology, including the field of “antenatal ophthalmology[17]” and “preimplantation genetic diagnosis for eye disease,[18]” which have been defined previously. A PubMed search using the terms “reproductive ophthalmology” did not return any results.

Results

The complex and dynamic genetic landscape underlying IEDs contributes toward their difficulty in diagnosis and treatment. Although not all cases will be this straightforward, here we present three cases of inherited eye disease with classic mendelian inheritance patterns managed with reproductive technologies.

Autosomal Dominant Inherited Eye Diseases

Autosomal dominant (AD) disease is characterized by the presence of a single heterozygous pathogenic variant affecting one allele on one of the 22 autosomes. Both sexes are equally affected, and typically a family history will be present. One of the most common genetic eye disorders with an AD inheritance is AD-retinitis pigmentosa.[19]

Autosomal dominant case study—Retinitis pigmentosa (RP) is a genetically and clinically heterogeneous group of IRDs with a prevalence of roughly one in 4,000 individuals.[19] Of all RP cases, 25% to 30% are AD. Autosomal dominant retinitis pigmentosa (AD-RP) causes night blindness and progressive visual field loss, which occurs because of predominant rod degeneration and subsequent cone and RPE degeneration.[20]

A 30-year-old woman with a strong maternal family history of RP and a diagnosis of RP (legally blind) at the age of six initially presented to our ophthalmology clinic with a desire to obtain further genetic testing in anticipation of future family planning. She had classic findings of optic nerve pallor, attenuated retinal vessels, and pigmented bone spicules in the retinal periphery with severe visual field constriction. We obtained genetic testing, which revealed a mutation (*p.*L523P) in the *KIF3B* gene associated with AD RP. She then proceeded with reproductive genetic counseling and IVF at the Stanford Reproductive Endocrinology and Infertility clinic. Ten blastocysts developed from one IVF cycle, and blastocyst biopsy revealed that three were euploid and unaffected. She and her husband decided to have a frozen embryo transfer of one of these unaffected embryos. Confirmatory chorionic villus sampling (biopsy of the placenta) was performed during the first trimester of pregnancy, confirming absence of the RP mutation in the fetus. This led to the successful birth of an unaffected healthy baby girl. She and her husband are considering undergoing another frozen embryo transfer with an unaffected embryo in the future, because they hope to have at least two children.

Autosomal Recessive Inherited Eye Diseases

Autosomal recessive disease is characterized by the presence of mutations affecting both copies of a gene residing on one of 22 autosomal chromosomes, leading to disease. With only one mutated copy, patients are typically clinically unaffected, and both sexes are equally involved. Parents are often unaffected, but there are exceptions where a parent has symptoms related to their mutation status.

Autosomal recessive case study—Achromatopsia is an AR disease that causes retinal cone dysfunction and symptoms of impaired color vision, nystagmus, and decreased visual acuity.[21] Implicated genes in achromatopsia include *CNGB3* and *CNGA3*, which encode cyclic nucleotide-gated channels located on the outer segment cell membranes of photoreceptors that play a crucial role in phototransduction.[22,23]

A 34-year-old female patient presented to Stanford Reproductive Health clinic interested in embryo cryopreservation. She and her husband had been previously identified as carriers for achromatopsia because of heterozygous pathogenic mutations in the gene *CNGB3*, and requested the preimplantation genetic testing to analyze the probability of their children

being affected by achromatopsia. She underwent counseling with our reproductive genetic counselor, followed by three rounds of oocyte retrieval and PGT-M. From all three cycles of IVF with PGT-M, 22 blastocysts were analyzed, and the ones that were viable for transfer back to the patient were as follows: two carrier males, one unaffected male, one unaffected female, and one carrier female. The couple is now proceeding with a transfer of the unaffected male blastocyst.

X-Linked Inherited Eye Diseases

X-linked disease is characterized by a pathogenic variant on an X (sex) chromosome. In X-linked recessive conditions, men are affected significantly more than women, but women may be affected because of variable X-chromosome inactivation (lyonization). One common IED with this inheritance pattern is congenital X-linked retinoschisis secondary to mutations in RS1.[24]

In X-linked dominant conditions, the female's healthy X chromosome does not readily compensate for the mutation; therefore, women and men can be affected. However, men often display a more severe phenotype, and the mutations are sometimes lethal early in life. Eye disorders with X-linked dominant inheritance include incontinentia pigmenti,[25] Aicardi syndrome,[26] and Goltz syndrome.[27]

X-linked case study—Goltz syndrome, also known as Focal Dermal Hypoplasia, is an X-linked dominant syndrome caused by mutations in the *PORCN* gene.[27,28] Ophthalmologic manifestations include chorioretinal colobomas, iris colobomas, nystagmus, strabismus, microphthalmia, anophthalmia, cataracts, and conjunctival and eyelid papillomas.[28]

A 33-year-old woman with a known history of Goltz syndrome with a history of focal dermal hyperplasia, squamous papillomas, and recurrent sinusitis was referred to Stanford reproductive health clinic from an outside clinic. She underwent one IVF cycle, nine blastocysts were biopsied, and PGT-M indicated that four were euploid and negative for Goltz syndrome. She and her husband decided to proceed with frozen embryo transfer of one of the four unaffected embryos. This led to the successful conception and delivery of an unaffected baby boy, a strong indication of the child being unaffected because this X-linked dominant condition would have been likely lethal to the male embryo. The boy was also tested postnatally to confirm the absence of the mutation. The patient and her husband are planning to have another frozen embryo transfer in the near future in the hopes of having another unaffected child.

Discussion

Managing IEDs with ART through collaborations between ophthalmology and REI specialists is not a novel practice.[29-31] The American Academy of Ophthalmology also released a seminal report about when and how to recommend genetic testing for IEDs.[32] The Academy's report included recommendations to offer genetic testing for patients with Mendelian disorders with causative genes that have been identified, to ensure genetic counseling from a physician or genetic counselor for these patients, to avoid direct-to-consumer testing, and to avoid testing for genetically complex disorders and untreatable

disorders.[32] However, uncertainty remains for how a multidisciplinary team (involving families, ophthalmologists, REI specialists, and genetic counselors) can practically approach this field in a collaborative fashion. Herein, we have outlined the rationale for this collaboration and provided examples of "reproductive ophthalmology" to demystify the process, increase utilization of available resources, decrease overall health care costs, and most of all, ***prevent*** the occurrence of vision loss.

The workflow we recommended begins with the ophthalmologist, who refers qualified patient(s) to a trained reproductive genetic counselor, who ultimately refers qualified patient(s) to an REI specialist to perform IVF with PGT (Figure 1). The ophthalmologist would ideally have some basic understanding of IEDs and ART as outlined in this manuscript to gauge the patient's general interest in the process; if not, we recommend referring to a colleague who has more experience in this area. In this recommended workflow, it is the responsibility of the ophthalmologist to perform genetic[2] and ancillary diagnostic testing, including evaluation of family members when applicable. Variants of uncertain significance and uncertain genotype–phenotype associations will need to be analyzed carefully by the ophthalmologist's genetic team. Having a high level of rigor in genotype–phenotype correlation is especially important today with the popularity of commercially available gene screening tests for this complex group of diseases to avoid false discovery rates and improper counseling.

The ideal deliverable from ophthalmologist to reproductive genetic counselor is a pedigree annotated with corroborating genetic and clinical findings. Fertility clinics can be found through referrals by local obstetricians and gynecologists, through the Society for Assisted Reproductive Technology online tool: https://www.sartcorsonline.com/members/Search, or through the Centers for Disease Control online tool: https://www.cdc.gov/art/artdata/index.html. Another helpful resource for clinicians and patients is the National Institute of Health (NIH) Genetic Eye Disease Database: https://rarediseases.info.nih.gov/diseases/diseases-by-category/9/eye-diseases.

At the next stage of the process, the ophthalmologist gives the information discussed above to a reproductive, prenatal, or infertility genetic counselor, who can discuss in detail reproductive options including technical limitations, and ethical and financial considerations. Finally, if patients or families are interested and are qualified candidates for PGT, the genetic counselor then refers them to an REI specialist to perform PGT, which combines two primary techniques: 1) IVF and 2) embryo genetic testing. Based on the results of embryo genetic testing, one low risk embryo is implanted at a time through standard IVF procedure, ideally resulting in the birth of an unaffected child. The current total cost of one complete cycle with PGT-M is approximately $20,000 to 30,000 USD, which may be variably covered by insurance and can often be justified with letters to the insurance company from the patient's primary care physician.

Patients may alternatively enter the "reproductive ophthalmology" workflow by directly scheduling an appointment with an REI specialist after 1) experiencing difficulty with conception, 2) having a child diagnosed with an inherited genetic disease and inquiring about potential options for future unaffected children, or 3) having self-identified as affected

by disease or as carrier(s) for disease through genetic carrier screening. The REI specialist can then refer the patient to reproductive genetics and ophthalmology to assess genotype–phenotype correlation and reproductive risks as needed.

Conclusions

Reproductive ophthalmology is an emerging collaborative field between REI specialists, reproductive genetic counselors, and ophthalmologists. Reproductive ophthalmology has the potential to play a significant role for couples with IEDs who want to conceive an unaffected child. Where gene therapy approaches are currently not often efficacious for AD, X-linked dominant, or mitochondrial-DNA-based conditions, the use of ART for ophthalmology is particularly exciting for families with IEDs (with or without affected children), because it can lead to the birth of an unaffected child, regardless of the inheritance type.

Because of the fact that the prevalence of carriers of an IRD-causing mutation is likely the highest across any group of human mendelian conditions (2.7 billion worldwide, ~1/3 of global population),[4] the significant economic impact of IED (IRDs alone cost the United States $31 billion USD per year), and the emerging popularity of ART (2% of all babies are currently born via IVF[14]), “reproductive ophthalmology” may represent a more cost-effective approach compared with current treatment options for these patients. This is especially true considering the implications of preventing disease transmission in sequential family lineages.

We conclude by mentioning that there are many challenging ethical considerations for all providers involved in ART and reproductive health. Although a full discussion of the ethics of reproductive technology is beyond the scope of this study, patients from different cultures, ethnicities, religions, and socioeconomic backgrounds will hold widely disparate beliefs about reproductive technology, and these beliefs must be respected. All members of the care team must be keenly aware of these factors and understand that there is not one approach that will be appropriate for every patient and family. It is important to note that this approach is not intended to “design” children with certain traits, because this is not currently possible even if there was parental desire to do so, but to prevent known and debilitating disease when the family expresses interest. We recommend having honest open-ended discussions designed to empower each individual patient and family member to make their decisions based on their own ethical, moral, and cultural values.

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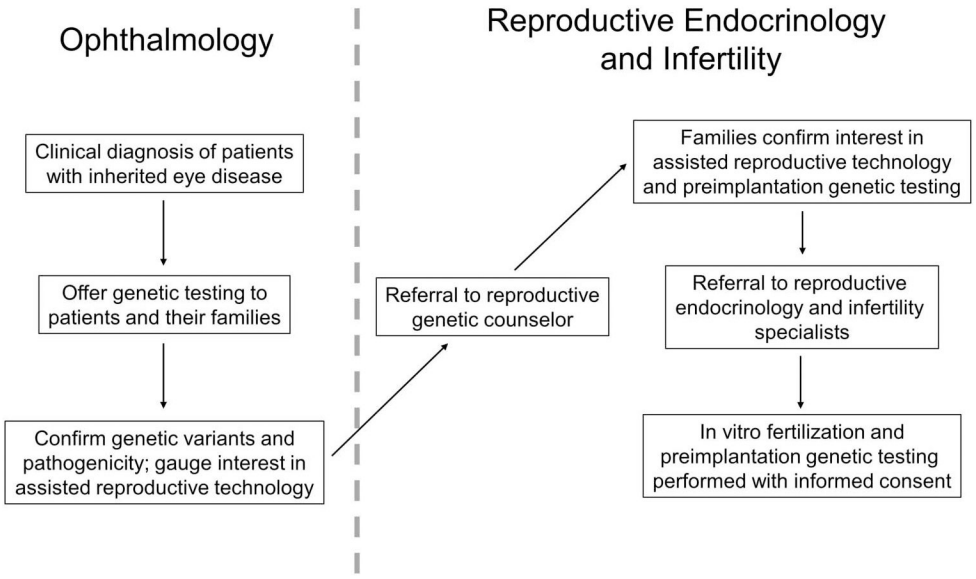

Fig. 1.

Framework for preimplantation genetic testing using a collaborative approach between ophthalmology and reproductive endocrinology and infertility for patients with IEDs.