

Research Article

Qualifications for Retinitis Pigmentosa and Leber Congenital Amaurosis Patients for Adeno-Associated Viral Gene-Replacement Therapy Clinical Trials

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Abstract

Introduction: This study identifies Retinitis Pigmentosa (RP) and Leber Congenital Amaurosis (LCA) patients at an Inherited Retinal Disease (IRD) clinic that qualify for ongoing or FDA-approved Adeno-Associated Virus (AAV) gene-replacement therapies. The goal is to demonstrate the benefits of genetic testing at the initial evaluation.

Method: A database for RP and LCA patients was curated and clinicaltrials.gov was used to search all ongoing or approved gene-replacement therapies between 1 January 2022 - 1 January 2023. Patients were evaluated for qualification based on the inclusion/exclusion criteria set by each trial.

Results: 199 RP and 31 LCA patients were included in the study. Our team identified six AAV gene-replacement therapy clinical trials and the FDA-approved Luxturna®. One hundred fifty-five patients underwent genetic testing and 89 patients had a pathogenic variant identified. A total of 15 patients qualified for one of the proposed trials. Three patients had a biallelic RPE65 mutation and two of them qualified for Luxturna®. All 11 patients with an RPGR mutation qualified for one of the three clinical trials that focused on this gene. Three patients had a c.2991+1655A>G mutation in CEP290 and two of them qualified one of two clinical trials for this gene.

Conclusion: Overall, ~10% of patients who had genetic testing qualified for one of the reviewed therapies. A total of 15 patients qualified for an AAV gene-replacement therapy. This study highlights the importance of promoting genetic testing for IRD patients, the need for earlier disease evaluation and the value of continual monitoring of disease progression.

Keywords: Adeno-Associated Virus; Inherited Retinal Disease; Retinitis Pigmentosa; Leber Congenital Amaurosis; Genetic Testing; Gene Therapy; Next Generation Sequencing; Whole Genome Sequencing; Whole Exome Sequencing; Variants of Uncertain Significance

Introduction

The use of genetic testing in ophthalmology has created an increased level of interest in the management of patients with Inherited Retinal Diseases (IRDs). More importantly, the expansion of genetic testing has spurred an interest in the development of gene-replacement therapies [1]. A retrospective series of 1000 consecutive families discovered disease-causing genotypes across 104 different genes in 760 families, demonstrating high sensitivity for genetic testing for IRD [2]. Panel-based Next Generation Sequencing (NGS) is the most cost effective first-tier method for molecular analysis within a diverse IRD population with the average out-of-pocket cost after insurance is less than \$100 using the Invitae genetic panel [3]. Several studies have shown diagnostic detection rates to be approximated at 60-70% while using NGS [3-6].

The list of pathogenic variants continues to expand with new discoveries [7]. As a result, recognition of genetic variant updates is required to maintain current findings for these genetic panels. It has been shown that whole genome sequencing (WGS) can uplift diagnostic findings by as much as 29% [8]. However, the costs and abundant amount of data can overwhelm its clinical use and reduce its weight as the dominant method of genetic testing in IRD clinics [2].

A problematic feature of genetic interpretation is the increased detection of Variants of Uncertain Significance (VUS). The understanding that patients may only have VUS on their genetic panel result indicates the need for further investigation of the underlying clinical suspicion, variant evidence and NGS panel content to establish a comprehensive genetic interpretation [9-10]. Our group previously found a diagnostic yield of 54.3%, [11] which is similar to what has been reported in the literature [12-14]. These results have suggested that, despite known complications that arise with non-diagnostic findings, NGS can serve as an effective method in determining diagnostic pathogenic variants for IRD patients seen at our clinic.

There are often restrictions for those who present in late stages of their disease presentation that make it difficult to find additional treatments, even with the emergence of gene-replacement therapy. Therefore, there is increased emphasis placed on screening suspected individuals earlier in life. The expansion of genetic testing, however, poses new stressors in clinical evaluation. One concern of incorporating genetic testing into a clinical practice is the limited training that ophthalmologists have with the interpretation and communication of these results with the patient and their families [15]. For this reason, genetic counselors are becoming an integral part of an IRD evaluation.

The goal of this study is to demonstrate how promoting genetic testing for IRD patients can help identify a suitable on-going, future planned, or already approved Adeno-Associated Viral (AAV) gene-replacement therapy trial. Results from ongoing clinical trials could establish gene therapy as the treatment for disease process reversal for inherited retinopathies. [16] Currently, the only FDA-approved gene therapy for IRDs is voretigene neparvovec-rzyl (Luxturna®), an adeno-associated virus, vector-based Subretinal (SR) gene therapy offered to patients with a biallelic RPE65 mutation-associated retinal dystrophy. Early successes in this clinical trial have built foundational support for the numerous ongoing and future recruiting gene-replacement therapy trials [17]. This research focuses on RP and Leber's Congenital Amaurosis (LCA).

Methods

Our cohort with syndromic and non-syndromic RP and LCA was studied retrospectively. The patients included were evaluated at the IRD Clinic at the University of Minnesota (UMN) Department of Ophthalmology and Visual Neurosciences between May 1, 2015 - August 4, 2022. This study was approved by our local IRB (STUDY00012478) and abides by the Declaration of Helsinki. The collected data did not exclude age, gender, or race. All patient data was checked to ensure that patients had not opted out of the research on the consent for service form. Clinical information collected using the REDCap software platform was used to create a clinical database to record genetic panel results.

The patients evaluated did not all have the same gene laboratory for genetic testing. This was often the case due to financial limitations, what panel previous family members used, or if there was a panel used to check for specific gene mutations/variants. Four common gene panels provided to our patients included Invitae Laboratory, Blueprint Genetics, Prevention Genetics and UMN Molecular Diagnostic Laboratory.

Once a genetic panel report returns, our ophthalmologists utilize their clinical assessment and genetic counseling to determine the diagnosis and management of the IRD. The American College of Medical Genetics and Genomics (ACMG) standards and guidelines for the interpretation of sequence variants was followed in this study to support medical decision making. [18] Our approach is to assess the pathogenic variant(s) to determine a confirmed diagnosis and to differentiate from those that only have clinical suspicion or of Variants of Uncertain Significance (VUS) of lower clinical suspicion. Patients that possessed only VUS were not followed up with Whole Genome Sequencing (WGS) or Whole Exome Sequencing (WES).

In this study, we focused on gene-replacement clinical trials to demonstrate the beneficial application of incorporating genetic testing in an IRD clinic. We did not limit the studies to any country. An extensive review of www.clinicaltrials.gov between January 1, 2022-January 1, 2023 was performed to identify the 'Recruiting', 'Not yet recruiting' and 'Enrolling by invitation' gene-

replacement clinical trials that were available for RP and RPE-associated LCA. Studies that were already completed by the time of the search were not included. The search function included keywords of “Retinitis Pigmentosa”, “Leber’s Congenital Amaurosis” and “Gene Therapy”. We also included Luxturna®, as it is already FDA-approved and patients can seek this option if they qualify. This approach will facilitate communications between providers and patients, by providing adequate up to date information regarding these clinical trials as a potential treatment if they qualify. Studies that included therapies other than gene-replacement or studies that were follow-ups from a previous gene-replacement trial were excluded. Clinical trials that were excluded are further detailed in the results section. Our team determined qualifications for a particular gene therapy clinical trial if:

1. A diagnostic variant was identified for patient’s condition based on the genetic panel and genetic counselor interpretation
2. The gene in question for the study matches the patient’s gene mutation or variant
3. If the patient meets the stated inclusion/exclusion criteria for an individual study. These three components were reviewed for all patients that underwent genetic testing.

Results

Gene Therapy Search

A search using www.clinicaltrials.gov identified six different gene-replacement clinical trials that are currently available for both RP and LCA and the FDA-approved Luxturna®. The list of therapies is included in Table 1. There were ten studies on clinicaltrials.gov under the search option “Retinitis Pigmentosa” and “Gene Therapy” that were excluded, as shown in Table 2. No clinical trials under the search option “Leber Congenital Amaurosis” and “Gene Therapy” were excluded. In addition, any trial listed as ‘Enrolling by invitation’ was not included, because these trials were either follow-ups from a previous trial enrollment or have a separate pre-requisite trial that must be fulfilled to be considered for enrollment. None of the patients within our cohort met these conditions.

Demographic Information

A total of 230 patients were included in this retrospective IRD cohort. The distribution consists of 31 patients with LCA and 199 patients with non-syndromic and syndromic RP. The RP cohort included 48 (24.1%) syndromic and 151 (75.9%) non-syndromic patients. The syndromic RP patients included Usher syndrome, Bardet Biedl syndrome, Cohen syndrome, nephronophthisis, Cardiofaciocutaneous syndrome and abetaproteinemia [1,2,4]. There were 114 males (49.6%), 115 females (50.0%) and one patient with an XY chromosomal arrangement did not identify with a binary gender (0.4%). 155 patients (67.4%) of those patients underwent genetic testing for both LCA and RP.

A summary of the commercial genetic panels that our cohort received and their corresponding pathogenic variant detection rate is presented in Table 3. It should be noted that any individual gene panel may range in the number of genes analyzed. The range may include anywhere between a single gene to >300 genes.

Invitae Laboratory was our most frequently used genetic testing laboratory at our IRD referral clinic. In general, depending on when the patient had genetic testing done, this gene panel analyzes anywhere between 248-330 genes that are most associated with IRDs. Single gene analysis was performed for patients with high suspicion for a particular gene of interest. For example, Harvard Center for Genetic and Genomics has a MYO7A full gene sequencing panel that tests for Usher syndrome type 1. Unique gene panels such as this are primarily located in the ‘Other’ section of Table 3.

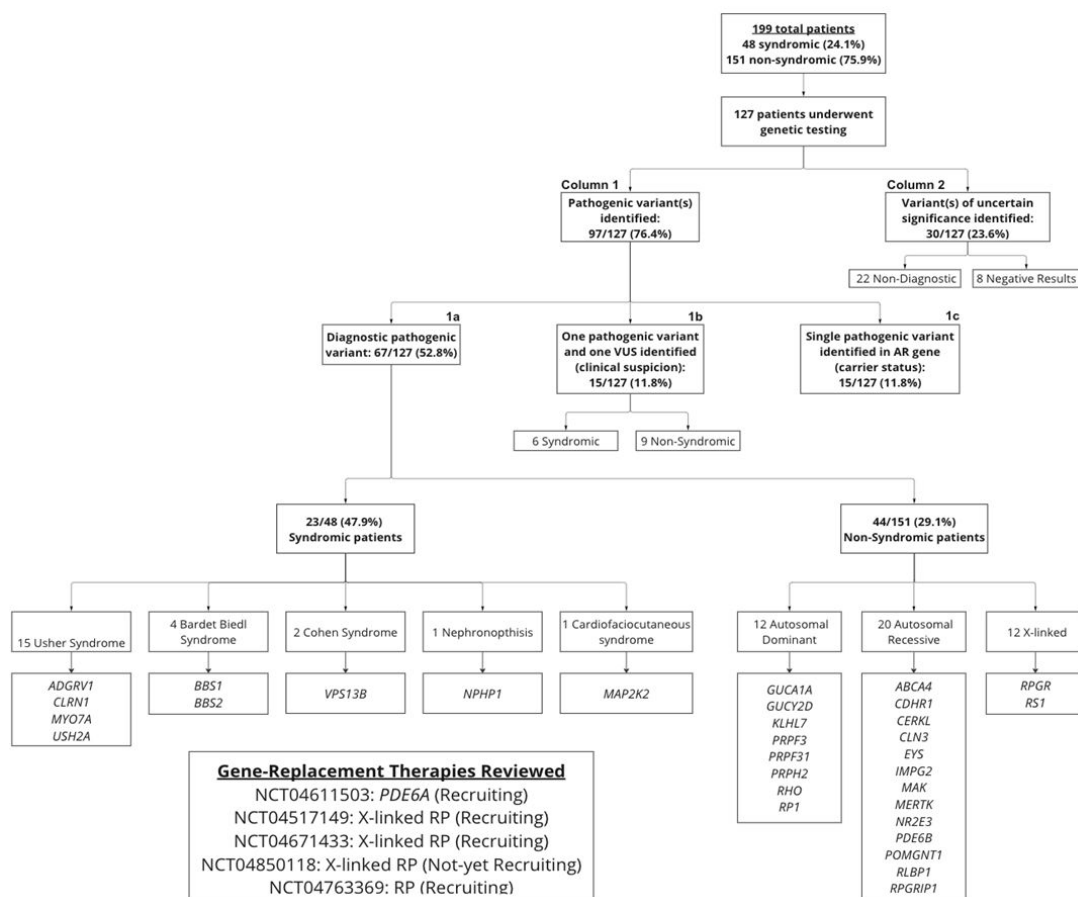


Figure 1: Genetic testing flowchart for retinitis pigmentosa patient cohort.

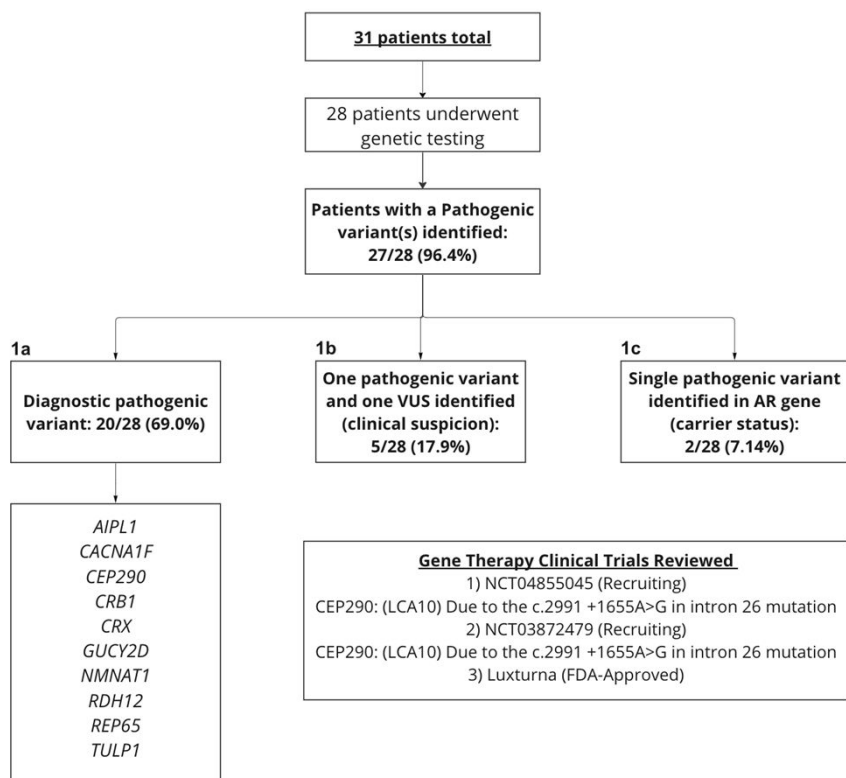


Figure 2: Genetic testing flowchart for leber's congenital amaurosis patient cohort.

Disease	Target	Phase	Status	Sponsor	NCT #	Description	# of patients qualified
RP	<i>PDE6A</i>	I/II	Recruiting	STZ eyetrial	04611503	Subretinal injection: rAAV.hPDE6A	0
RP	<i>RPGR</i>	III	Recruiting	MeiraGTx UK II Ltd	04671433	Subretinal injection: AAV5-RPGR	11
RP	<i>RPGR</i>	II/III	Not Yet Recruiting	Applied Genetic Technologies Corp	04850118	Subretinal injection: AGTC-501	5
RP	<i>RPGR</i>	I/II	Recruiting	4D Molecular Therapeutics	04517149	Intravitreal injection: 4D-125	4
LCA	<i>CEP290</i> : c.2991+1655A>G in intron 26	II/III	Recruiting	ProQR Therapeutics	04855045	Intravitreal injection: Sepofarsen	1
LCA	<i>CEP290</i> : c.2991+1655A>G in intron 26	I/II	Recruiting	Editas Medicine, Inc.	03872479	Subretinal Injection: EDIT-101	2
LCA	<i>RPE65</i>	Luxturna ® (FDA-approved clinical trial)				Subretinal injection: voretigene neparvovec-rzyl	2

Table 1: Interventional gene-replacement therapy clinical trials.

NCT #	Reason for Exclusion
NCT04639635	This trial is not a gene-replacement intervention and is only a natural history progression study associated with <i>CNGB1</i> mutations.
NCT04448860	This trial assesses the performance of behavioral locomotion tasks that is used to measure a therapeutic benefit for new gene therapies.
NCT02759952	This trial is an observation study of <i>PDE6A</i> -related RP.
NCT02465749	This trial focuses on continuous oxygen and does not involve any form of gene-replacement therapy.
NCT05085964	This trial focuses on Usher Syndrome Type 2. It was not included because it is an extension trial for patients who previously participated in a QR-421a clinical study. None of our patient cohort had completed a QR-421a trial.
NCT04312672 and NCT04794101	These trials are follow-ups from previous X-linked <i>RPGR</i> gene therapy clinical trials, and, thus, were not included in this study.
NCT03584165	This trial is follow-up from gene-replacement therapy BIIB111.
NCT04763369	This trial focuses on an injection of stem cells and not gene-replacement therapy, in the sub-tenon or suprachoroidal space of the eye for the management of RP.
NCT03326336	This trial focuses on optogenetic engineering and not AAV gene-replacement therapy.

Table 2: List of excluded clinical trials.

Gene Panel*	# Patients Utilized	# Diagnostic Pathogenic Variant	Pathogenic Detection Rate (%)
Invitae Laboratory	78	36	46.2
UMN NGS	33	24	72.7
Prevention Genetics	12	6	50.0
Blueprint Genetics	9	8	88.9
Other	23	15	65.2
*Each panel may range from 1 to >300 genes tested			

Table 3: Patient genetic panel utilization and pathogenic detection rate.

Retinitis Pigmentosa Cohort Overview

A total of 127/199 (63.8%) syndromic and non-syndromic RP patients had genetic testing completed at the time of this study. 97/127 (78.0%) patients had at least one pathogenic variant on their genetic report. Of those patients, 67/127 (52.8%) patients had a diagnostic variant (Figure 1. Column 1a). This 52.8% reflects the diagnostic yield for our RP cohort. The remainder of patients who did not have a diagnostic pathogenic variant identified were considered either as having clinical suspicion with one pathogenic variant and one VUS identified (11.8%) or having carrier status with only a single pathogenic variant identified in an autosomal recessive gene (11.8%) (Fig. 1). The criteria for a diagnostic pathogenic variant were determined based on clinical examination and imaging, interpretation of the patient's genetic panel and evaluation by a genetic counselor at the UMN. Additionally, findings of only VUS were found in 22/127 (17.3%) patients, 21 of them being non-diagnostic and one with clinical suspicion (Fig. 1). The final 8/127 (6.3%) patients had only negative results for their genetic report (Fig. 1). The inheritance pattern distribution in our cohort included 14/69 (20.2%) autosomal dominant, 42/69 (60.9%) autosomal recessive and 12/69 (17.3%) X-linked RP (Fig. 1). Within these inheritance patterns, 11/12 (91.7%) of the patients with X-linked RP had a diagnostic RPGR mutation. Figure 1. also shows all diagnostic pathogenic or likely pathogenic variants that were found in our RP cohort and the gene therapy clinical trials that were reviewed.

There are six gene-replacement clinical trials that were reviewed for the 67 patients that had a diagnostic pathogenic or likely pathogenic variant(s) confirmed from genetic testing, clinical assessment and genetic counseling. The studies included one trial that centered on PDE6A gene mutation and three trials for X-linked RP (Fig. 1). The PDE6A gene-replacement is phase I/II trial that consists of single subretinal injection of rAAV.hPDE6A. No one in our RP patient cohort had PDE6A-related retinal dystrophy. The next three studies are for X-linked RP. We had 12 patients diagnosed with non-syndromic, X-linked RP (Fig. 1). 11 of those patients had the RPGR mutation, while the remaining patient had an RS1 mutation, that is associated with X-linked juvenile retinoschisis, however had a diagnosis of RP. Those 11 patients were analyzed amongst the three gene-replacement clinical trials that are currently available for the RPGR mutation. The first RPGR gene-replacement clinical trial (NCT04671433) had 10/11 (90.9%) of our patients qualify. It is a phase III randomized, controlled study that intervenes with bilateral, subretinal administration of AAV5-RPGR. The second study (NCT04850118) had 5/11 (45.5%) patients qualify. This study is in phase II/III and is a randomized, controlled, masked, multi-center study evaluating 2 doses of AGTC-501. The final X-linked RPGR study (NCT04517149) had 4/11 (36.4%) patients qualify. This is phase I/II study that will evaluate the safety, tolerability and preliminary clinical efficacy of a single Intravitreal (IVT) injection of 4D-125 at two dose levels in one or both eyes. The other portion of this study will gather data in an observational phase Natural History Cohort to evaluate disease progression.

Leber's Congenital Amaurosis Cohort Overview

A total of 28/31 (90.3%) patients underwent genetic testing completed at the time of this study. 27/28 (96.4%) patients who had genetic testing had a pathogenic or likely pathogenic variant that was identified. A total of 20 patients from the 27 patients were found to have a pathogenic or likely pathogenic variant(s) that was diagnostic for their IRD. Overall, this suggests that the detection rate is 69.0% (Fig. 2). The other patients who did not have a diagnostic variant identified included five patients who had clinical suspicion with one pathogenic variant and one VUS identified (17.9%) (Fig. 2). The remaining two patients had carrier status with only a single pathogenic variant identified in an autosomal recessive gene (7.14%) (Fig. 2). Fig. 2. also shows all diagnostic variants that were found in our LCA cohort and the gene therapy clinical trials that were reviewed.

There are two gene-replacement clinical trials and Luxturna® that were reviewed for the 20 patients that had a diagnostic genetic testing, clinical assessment and genetic counseling. Both on-going, recruiting clinical trials focus on the CEP290 gene mutation. They center on LCA10 due to the c.2991+1655A>G mutation. The first clinical trial (NCT04855045) consists of two parts: an open-label dose escalation part, followed by a double-masked randomization. It is a phase II/III trial that evaluates the safety and tolerability of sepfarsen administered via Intravitreal (IVT) injection in pediatric subjects (<8 years of age). 1/4 (25%) patients with this gene mutation qualified for this study. The other CEP290 gene-replacement clinical trial (NCT03872479) is a phase I/II, open-label, single ascending dose study to evaluate the safety, tolerability and efficacy of the EDIT-101 subretinal injection in the adult and pediatric participants. With the expansion of age limitations, 2/4 (50%) patients with this same mutation qualified for this gene-replacement study. The final study we evaluated our patients for was Luxturna® (voretigene neparvovec-rzyl). We had 2/3 (67%) patients with RPE-65 associated RPE that qualified for this study.

Retinitis Pigmentosa Gene Therapy Review

There were four clinical trials that focused on gene-replacement that were analyzed in this study. To recapitulate, one trial examines the PDE6A mutation and the three remaining trials on X-linked RPGR. Trial NCT04611503 will not be discussed since our patient population does not contain the PDE6A gene mutation. The following three gene-replacement therapy trials all focus on X-linked RPGR. We evaluated the same 11 patients that had this specific mutation.

- NCT04671433: This trial only includes inclusion and no exclusion criteria. All 11 patients with X-linked RPGR qualified for this study. Participants can be either male or female and be >3 years of age. The X-linked RP also must be confirmed by a retinal specialist and has a predicted disease-causing sequence variant in RPGR confirmed by an accredited laboratory
- NCT04850118: This trial had five patients qualify. The only exclusion is that the participant must not have another known retinal disease variant or previously received an AAV gene therapy product, none of which X-linked patients had. The age restrictions were between 8-50 and the patient must be male. In addition, the gene panel report must have at least one documented pathogenic or likely pathogenic variant in the RPGR gene within exons 1-14 and/or ORF15 (ORF15 is a highly repetitive, purine-rich DNA region). The last inclusion point is to have a BCVA no better than 75 letters (20/32) and no worse than 35 letters (20/200) in the study eye. Three of the patients fell out of the required age range for this study. One patient was excluded due to female status. The remaining two patients did not have a BCVA worse than ≤78 ETDRS letters
- NCT04517149: This trial had four patients qualify. The exclusion criteria include if the patient received any past AAV treatment or if there are pre-existing eye conditions or surgical complications that would preclude participation in an interventional clinical trial or interfere with the interpretation of study endpoints. The patient must male and be ≥12 years old. Three patients did not qualify based on the age requirements. Two patients had a BCVA not worse than ≤78 ETDRS letters. The final two patients had a BCVA worse than ≥ 34 ETDRS letters

Leber's Congenital Amaurosis Gene Therapy Review

There were two clinical trials and the FDA-approved Luxturna® gene-replacement therapies that were viewed in this study. The two clinical trials that focused on CEP290 gene c.2991+1655A>G mutation each had the same four patients that underwent further investigation for qualification.

- NCT04855045: One patient met the inclusion/exclusion criteria. One patient displayed a separate variant from the required c.2991+1655A>G mutation. Another patient was older than the required age presentation of <8 years of age. The final patient had too advanced disease presentation based on a Best Corrected Visual Acuity (BCVA)
- NCT03872479: Two patients met the complete inclusion/exclusion criteria required by the study. To note, one of the patients that qualified for this trial also qualified for the previous trial mentioned. The additional patient who met qualifications was based on the inclusion criteria of the age requirement being >3 years of age. One patient did not qualify again due to the incorrect mutation of study. The other remaining patient also did not qualify due to advanced disease presentation established based on the inclusion criteria of measured visual acuity
- Luxturna®: Three of our patients with LCA had the RPE65 gene variants that were diagnostic for their condition. The gene alone warranted further investigation for the only FDA-approved gene-replacement therapy. These patients were sent to be evaluated as candidates for this therapy. Two of the patients qualified and have already received treatments. The remaining patient was rejected for the therapy based on a too advanced disease presentation

Discussion

Our study reviewed six current AAV gene-replacement therapy clinical trials and the FDA-approved Luxturna® for our patients who underwent genetic testing and found a variant diagnostic towards their IRD. As we recognize there are many potential variants responsible for IRDs, there is still work in progress to address all those that cause syndromic and non-syndromic RP and LCA. The gene-replacement clinical trials that are currently available at the time of this paper represent PDE6A, RPGR, CEP290 and RPE65. In total, the number of clinical trials available for RP and LCA patients remain scarce. This places limitations for patients who qualify based on having the appropriate gene of interest and meeting the inclusion/exclusion criteria. In our cohort, the number of patients that qualify after applying the specific clinical trial qualifications for gene-replacement therapy was ~10%.

Qualifications for each proposed trial strictly followed the inclusion and exclusion criteria. It was often noted that each trial required a certain disease presentation. This was determined by either BCVA or diagnostic testing, such as OCT or ERG. Patients who presented at the initial clinical evaluation with advanced disease presentation had to be excluded. Conversely, clinical trials may also require a certain degree of visual impairment before patients can be considered. In these instances, patients with earlier disease presentation and possessing the pathogenic gene or variant studied in the clinical trial, would need annual screenings to monitor disease progression for minimum threshold of participation. This same notion would apply to the individuals who were excluded due to underage requirements. The data collection timeframe set by each study should be closely reviewed with patients who are underage but otherwise qualify for the study. We currently have three patients who will meet requirements for studies NCT04517149 and NCT04850118 once minimum age requirements are met. Those patients can then be placed into the qualification category once either the age requirements are met or the minimum age to participate is lowered.

Our retinal ophthalmologists encourage patients to learn more about their condition by adding genetic testing and to keep them up to date on current research and clinical trials. It is the patient's choice to contact the clinical trial coordinators for additional information. Despite this, the data demonstrates the importance of promoting genetic testing for IRD patients at the initial visit. Knowing that ~10% of our patients who underwent genetic testing will have a potential interventional treatment available can change the quality of life for patients living with an IRD.

The use of NGS has shown to be beneficial at our institution. We obtained diagnostic results for 54.3% of the RP cohort and 71.4% in the LCA cohort. This difference in diagnostic yield could partially be attributed to the amount of currently known genes that are contributory to each respective condition. The various gene panels (Table 3) exhibit a wide range of tested genes. These include anywhere between 1 and >300 genes. Many of our patients had the Invitae Laboratory panel as their primary laboratory. This gene panel tests for hundreds of genes. The numerous variants can account for the ones that are most recognized in non-syndromic RP yet can show results that are either likely pathogenic or VUS. To reiterate, the likely pathogenic variants can still be diagnostic. Conversely, gene laboratories listed as 'Other' in Table 3 may test for specific mutations that will likely be diagnostic if there is a high suspicion for a particular syndromic RP condition.

Another factor to consider is the continual gene panel updates. Patients who had their genetic testing performed in 2015 may not have the most updated version of their respective gene panel. For example, earlier Invitae Laboratory panels tested for 248 genes and now include over 330 genes. Thus, our detection rate may be underestimated if newer identified genes are not accounted for in patients who had older versions of genetic testing. This suggests that patients with non-diagnostic results may benefit from repeat genetic testing with their same gene panel or other panels that account for genes not previously covered.

The other possible option to account for the numerous VUS would be to consider testing immediate family members. If the results were to show matching VUS between closely related individuals, there would be further discussion with genetic counseling of a possible diagnostic variant [19]. For our institution, this has been hard to accomplish due to patient travel distance, concern over costs, or lack of follow-up.

It is also important to consider that none of the proposed trials focus on treatment for autosomal dominant RP. Consequently, our patients who are non-syndromic and are found to be autosomal dominant may be reluctant to undergo genetic testing. This, however, is not the case for X-linked RP patients caused by the RPGR gene, as there are currently several ongoing trials.

Our study not only supports the importance of genetic testing, but also the crucial aspect of developing a comprehensive IRD database. We could record many patient disease presentations and genetic results through REDCap to analyze the data for future clinical trial qualification. We can also further identify more prevalent genes found within our demographic region. In this study, we focused exclusively on RP and LCA. This is largely because these two conditions are more frequently encountered at our clinic. The expansion of other types of IRDs with respect to genetic testing and available AAV gene-replacement therapies can be investigated in future studies, such as achromatopia and x-linked retinoschisis [20].

Close correspondence with genetic counseling aided in the diagnosis when the genetic report had only probable pathogenicity or unspecified findings of clinical significance. This can be also addressed by promoting more updated genetic panel testing. Together, this will help patients to be considered for any of the gene-replacement trials. Our results further suggested that there are patients who almost qualified for either gene-replacement therapy trials or Luxturna® but were excluded due to advanced disease presentation. Our goal is to take a proactive stance to confirm genetic diagnosis as more genetic testing options, advancements and cost-saving methods become readily available. We advocate for yearly eye examinations for patients that have not yet qualified due to minimal disease progression. Patients could also choose to get notifications once they either meet minimum age requirements or other visual symptoms worsen to the point where they qualify for inclusion criteria.

Conclusion

A total of 155/230 (67.4%) patients underwent NGS. A diagnostic variant was found in 87/155 (56.1%) patients. Individually, 63.8% of RP patients and 90.3% of LCA patients underwent genetic testing. It was subsequently found that 54.3% and 71.4% of patients were diagnostically confirmed by genetic testing, respectively. 15/87 (17.2%) of the diagnostically confirmed patients via genetic testing qualified for gene-replacement therapy. If looking at the perspective for all patients who underwent genetic testing, 15/155 (~10%) of patients qualified. This means that approximately one in ten individuals that underwent NGS, had a genetic testing result that qualifies for either a clinical trial or Luxturna®. Looking at only patients who underwent genetic testing within the RP and LCA cohorts reflected 11/127 (8.7%) and 4/28 (14.3%), respectively.

In summary, genetic testing is the first essential step to determine AAV gene-replacement therapies. The availability of these clinical trials remains limited. For this reason, it is crucial to establish an organized IRD database to monitor patient disease progression and genetic results. This can help keep track of patients who qualify or will potentially qualify with the hopes of finding a treatment for an incurable disease.

Conflict of Interest

The authors have no conflict of interest to declare.

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