The Landscape of Clinical Trials Research in Inherited Ophthalmic Disease

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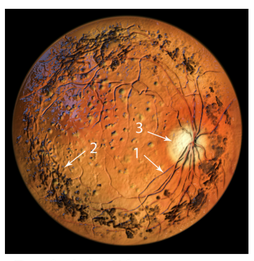
Background & Aim

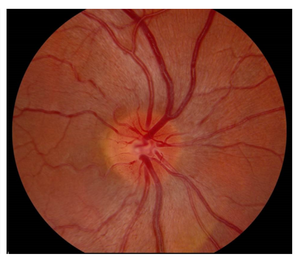
- Recent advancements in the understanding of molecular and genetic causes of genetic eye diseases have enhanced the possibility of therapeutic interventions
- Success is dependent on the ability to identify precise targets for intervention with maximum therapeutic effect and minimum harmful side-effects
- We aim to review current clinical trials of eight inherited genetic eye diseases with established molecular pathology, and identify opportunities for future research and therapeutic development

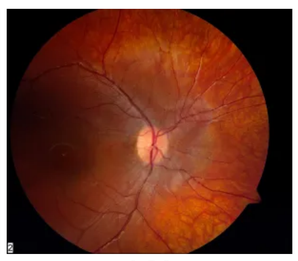
Methods

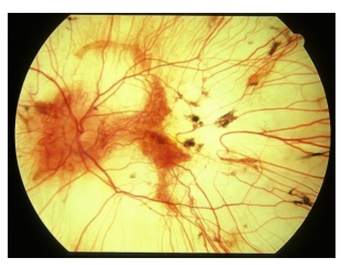
Data analysis of the clinical trials database on clinicaltrials.gov with keywords of eight common, genetically tractable inherited eye diseases and their common molecular targets were performed from 20/3/2021 to 31/12/2023.

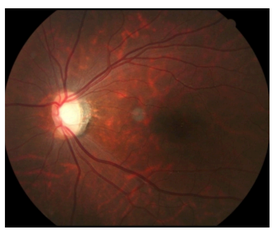
Key words include Retinitis Pigmentosa (RP), Leber Hereditary Optic Neuropathy (LHON), Leber Congenital Amaurosis (LCA), Choroideremia, Autosomal Dominant Optic Atrophy (ADOA), Retinoschisis, Usher syndrome (USH) and Stargardt disease (STGD).

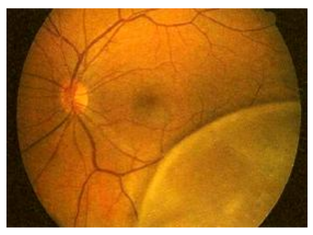

Retinitis Pigmentosa

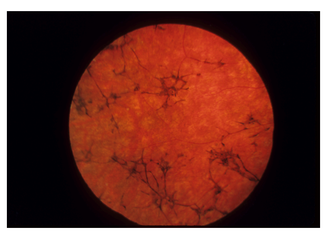

LHON

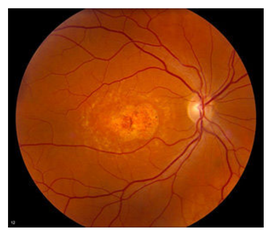

LCA


Choroideremia

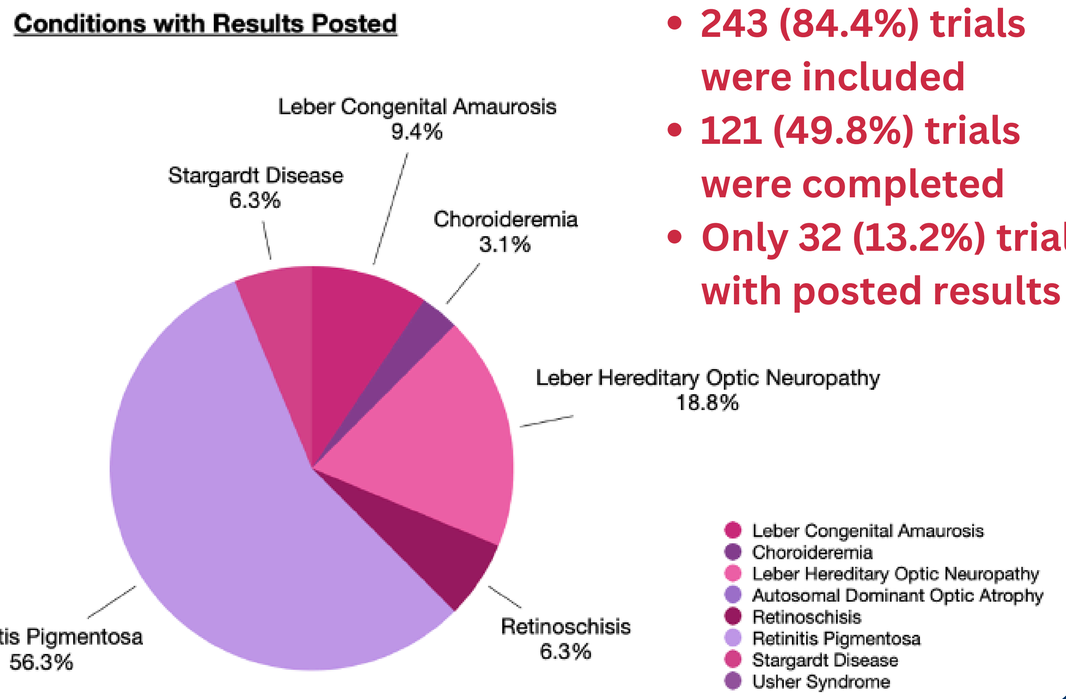

ADOA


Retinoschisis


Usher Syndrome


Stargardt Disease

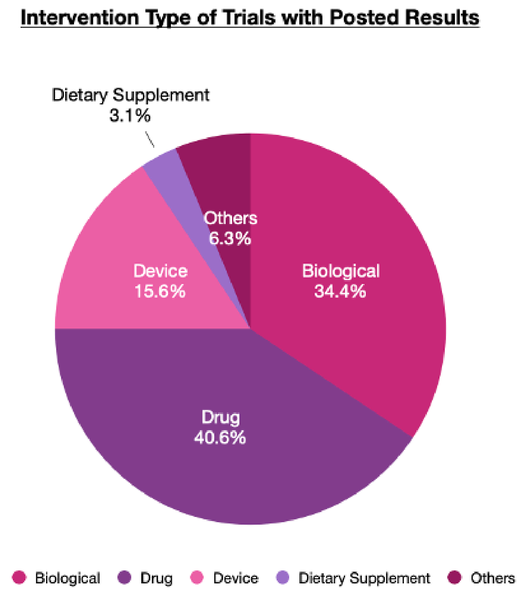
Result: Overview of Number of Trials



- 243 (84.4%) trials were included
- 121 (49.8%) trials were completed
- Only 32 (13.2%) trials with posted results

Result: Intervention Types

- Drug intervention trials are the most common (102 trials, 42.0%)
- Biological intervention (49 trials, 20.2%)
  - Including gene therapy, stem cell therapy, transplantation
- Device intervention (36 trials, 14.8%)



Result: Research Focus for Genetic Therapy

- Majority of the genetic studies focus on retinitis pigmentosa (55.1%/ 38 trials), LCA (15.9%/ 11 trials) and choroideremia (11.6%/ 8 trials)
- 37 of all trials (53.6%) use adeno-associated viral vector approach to deliver gene replacement therapies
- Stem cell and transplant therapy are mainly used in retinitis pigmentosa and Stargardt disease
- None of the ongoing registered genetic trials are exclusively recruiting patients with autosomal dominant inheritance

Condition	# of Genetic Trials	Gene Therapy Study Approach
Choroideremia	8	Adeno-associated viral vector (8 trials)
Retinitis Pigmentosa	38	Adeno-associated viral vector (11 trials) Injection of virally carried Multi-Characteristic Opsin I (2 trials) Genetic analysis of patients (1 trial) Skin biopsy for retinal degeneration (1 trial) CPK850 (RLBP1 stimulant drug) gene therapy (1 trial) Transplantation: Platelet rich plasma transplant (3 trials) Stem cell therapy (17 trials)
Leber Congenital Amaurosis (LCA)	11	Adeno-associated viral vector (9 trials) Phenotyping and genotyping (1 trial) Gene replacement therapy (1 trial)
Leber Hereditary Optic Neuropathy (LHON)	5	Recombinant adeno-associated viral vector (5 trials)
Retinoschisis	4	LX103 treatment for X-linked retinoschisis (1 trial) Adeno-associated viral vector (2 trials) ATSN-201 Gene therapy (1 trial)
Stargardt Disease	3	Sub-retinal transplantation (2 trials) Intravitreal injection of gene therapy (1 trial)
Autosomal Dominant Optic Atrophy (ADOA)	0	
Usher Syndrome	0	

Table 1. Breakdown of the type of gene therapy study.

Conclusion

- A low percentage of results were posted for completed trials
- There are knowledge gaps in gene therapy for autosomal dominant conditions. It is challenging but has great potential for research.
- Looking ahead, trial emphasis should focus on efficient 'bench-to-bedside' transition
- The results of these trials will enable a better understanding of the potential to develop treatments for these conditions

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