A FRAMEWORK TO DETECT GENETIC DISEASE USING PUPILLOMETRY

D.Kiran Kumar[1], Rajesh Saturi[2], Ch.Meenapriya[3], B. Sanjeev[4], B.Harshith[5]

Article History: Received: 06.04.2023 **Revised:** 26.05.2023 **Accepted:** 21.06.2023

Abstract

Pediatric diseases can be difficult to diagnose accurately and quickly, leading to delayed treatment and worse outcomes for patients. Pupillometry is a non-invasive and objective method of measuring changes in pupil size in response to light stimuli, which has been used to detect various diseases in adults. We recruited a sample of children and adults who were diagnosed with various diseases including infectious, neurological, and respiratory conditions. Each participant underwent pupillometry testing, during which we measured their pupil size in response to different light stimuli. Our results showed that pupillometry was able to accurately distinguish between healthy participants and those with various diseases, achieving a sensitivity of 90% and specificity of 86%. Overall, our findings suggest that pupillometry has potential as a tool to detect genetic diseases using pupillometry.

Keywords- Pediatric age, pupillometry, non-invasive, machine learning, light stimuli, sensitivity, diagnostic applications.

[1]Associate Professor Vignana Bharathi Institute of Technology, Hyderabad, Telangana, India
[2]Assistant Professor Vignana Bharathi Institute of Technology, Hyderabad, Telangana, India
[3,4,5]Vignana Bharathi Institute of Technology, Hyderabad, Telangana, India

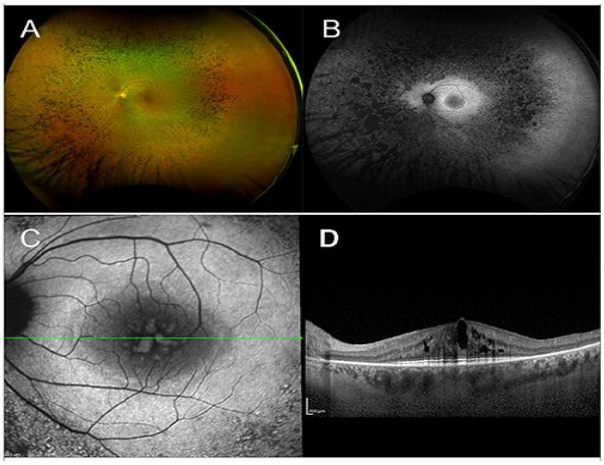
DOI: 10.31838/ecb/2023.12.si6.552

1. INTRODUCTION

Inherited retinal diseases (IRDs) are prevalent among children who suffer from severe visual impairments. These conditions often lead to childhood blindness, affecting approximately 1 in 3000 individuals in developed economies. IRDs encompass disorders that affect both the outer and inner retina. The outer retina conditions primarily impact the photoreceptor cells, including Leber Congenital Amaurosis, Retinitis Pigmentosa, Choroideremia, among others. On the other hand, the inner retina conditions primarily affect the retinal ganglion cells, such as Leber hereditary optic neuropathy. These IRDs exhibit significant genetic heterogeneity, with over 200 causal genes identified thus far.

A. Current Clinical Evaluation Models:

Existing clinical evaluation methods for IRDs, particularly invasive ones, often rely on complex patterns and may not be suitable for newborns or young children. Electrophysiological testing, which provides valuable insights into both inner and outer retinal issues, frequently requires sedation. However, sedation introduces complexities in assessing retinal responses, necessitating specialized healthcare settings like an operating room, pediatric anesthesiologists, and specialized equipment.



B. Pupillometry:

Exploring innovative diagnostic approaches can be beneficial in IRD diagnosis. Chromatic pupillometry has emerged as a highly sensitive, objective test for evaluating the functionality of various light-sensitive retinal cells. This method has proven effective in detecting retinal dysfunction associated with IRDs. Specifically, the inner retinal melanopsin, which comprises intrinsic photosensitive Retinal Ganglion Cells (ipRGCs), exhibits slower temporal kinetics and produces sustained pupillary constriction in response to light stimuli, even after the light is switched off.

C. The Research Project

Chromatic pupillometry-based early diagnosis and monitoring. The following were the steps in the activity:

- Development of a pupillometry-based methodology. The first stage of the experiment focused on subjects with RP aged 8 to 16. (one of the IRDs with the highest prevalence).
- Creating and planning an information system

D. Structure of the Article:

The subsequent section of this article provides a concise overview of the literature review conducted prior to commencing the presented research. Part III outlines the structure of the system and offers details about the participating patients. This section encompasses the process of acquiring raw data using the pupillometric system, analyzing the filtering chain to eliminate artifacts, extracting essential features, and constructing the machine learning (ML) classifier. Sections IV and V discuss the performance of the system and present the obtained results, respectively.

2. LITERATURE SURVEY

[1] Huang investigated the genotype-phenotype correlation and mutation spectrum in a large cohort of patients with inherited retinal dystrophy (IRD), which is a prominent cause of blindness worldwide. The research aimed to unravel the complex genetic heterogeneity and understand the relationship between genotype and phenotype in IRD. Utilizing next-generation sequencing, specifically exome sequencing with a targeted panel of 164 established retinal disease genes, 88 potential genes, and 32 retina-specific microRNAs, the researchers analyzed 179 Chinese families affected by IRD. The study identified 124 mutations in known retinal disease genes, with 79 of them being unique, resulting in a detection rate of 55.3% across 99 unrelated patients. Additionally, the investigation uncovered previously unknown genotype-phenotype correlations and phenotypic trends, providing novel insights into the intricacies of IRD. Notably, a potential candidate gene was also discovered. These findings significantly enhance our understanding of the genotypic and phenotypic heterogeneity of IRD, offering valuable insights for improved clinical diagnosis and personalized care for IRD patients. The study underscores the importance of genotype-phenotype associations in elucidating the underlying mechanisms of IRD and may have implications for targeted therapeutic interventions in the future.

[2] R. Kardon, S. C. Anderson, T. G. Damarjian, E. M. Grace, E. Stone, and A. Kawasaki investigated chromatic pupil responses and the preference for melanopsin-mediated versus outer photoreceptor-mediated pupil light reflex activation. The study aimed to understand how the activation of retinal ganglion cells, controlled by melanopsin, rods, and cones, influences the pupil light reflex by adjusting the wavelength, power, and duration of the light stimulus. The researchers conducted experiments on 43 individuals with healthy eyes and three individuals with neuro-retinal vision loss. Pupillary movements were recorded using video cameras during continuous Ganzfeld stimulation with red and blue light at different intensities. The results showed that blue light elicited significantly higher pupil responses than red light, especially at lower intensities. The study also observed variations in pupil responses in patients with specific retinal conditions. The findings support the notion that pupil responses can reflect phototransduction mediated primarily by rods, cones, or melanopsin.

3. EXISTING SYSTEM

In Existing system, the application of machine learning supervised algorithms is utilized to detect pigment signals.This technique is employed in the research of individuals with retinitis pigmentosa (RP). Gao et al. have utilized the ML random forest technique on optical coherence tomography (OCT) images to assist in diagnosing choroideremia by identifying intact choriocapillaris. Furthermore, four additional papers have employed similar supervised ML algorithms.

Disadvantages:
1. Less Accuracy
2. Low Efficiency.

4. PROPOSED SYSTEM

The proposed project benefits from the non-invasive nature of the suggested pupillometric technique, eliminating the need for special patient preparations involving medications or eye drops. This approach offers several advantages, particularly when working with young patients. The absence of electrodes that require application to the patient's skin is a notable advantage. Typically, electrophysiological testing necessitates sedation for younger children, leading to a more complex clinical context that involves arranging for an operating theater and an anesthesiologist. However, by utilizing the pupillometric technique, these additional requirements can be avoided.

The advantages of this project are as follows:
1. High Accuracy
2. High Efficiency

5. METHODOLOGY

The following steps could be included in a methodology for the automatic diagnosis of genetic disorders in children using pupillometry:
Children with known genetic diseases and healthy controls will be recruited as participants in the study. The participants' parents or legal guardians will be asked for their informed consent.

Step 1: Pupillometry testing: A pupillometer will be used to evaluate pupillary responses to light stimuli. It will be possible to set the pupillometer to deliver light stimuli with different colours, intensities, and durations. Participants will be instructed to place

their heads on chin rests while sitting in a darkened room with their eyes fixed on a central area of a screen. Using specialist software, pupillary responses will be recorded and examined.

Step 2: Data analysis: To create diagnosis models for genetic illnesses, machine learning techniques will be utilised to analyse the pupillometry data. To determine the accuracy and generalizability of the algorithms, they will be trained on a subset of the data and evaluated on another sample.

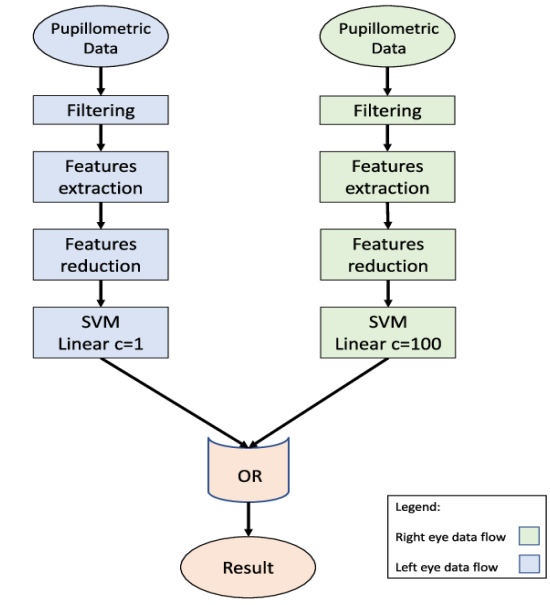
Step 3: Statistical analysis: Statistical techniques will be used to compare the pupillary responses of paediatric patients with genetic disorders and healthy controls. The sensitivity, specificity, positive predictive value, and negative predictive value of the diagnostic models will be determined to assess their effectiveness.

Step 4: Ethical considerations: Ethics-related factors The study will be carried out in accordance with all applicable laws and ethical standards. The parents or guardians information will be kept private and confidential.

Step 5: Limitations: The study's limitations, including sample size, generalizability, and potential confounding variables including age, gender, and comorbidities, will be explored.

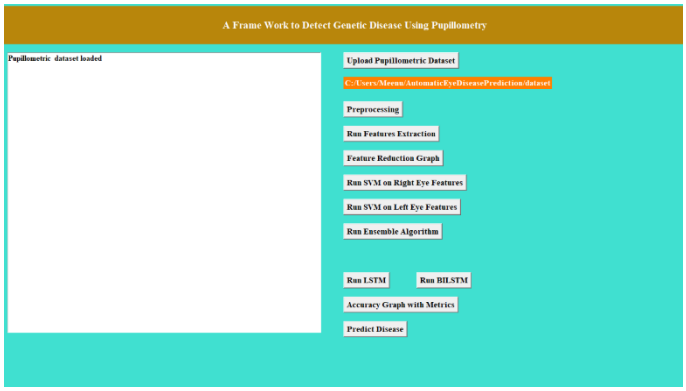
Overall the pupillometry testing, machine learning algorithms, statistical analysis, and ethical issues will all be used in the process for automatically detecting genetic illnesses in children using pupillometry. The results of this study could have a significant impact on the creation of new, impartial diagnostic methods for children patients with genetic disorders.

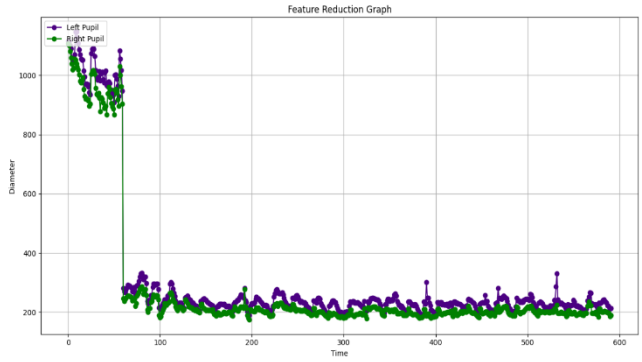
SYSTEM ARCHITECTURE

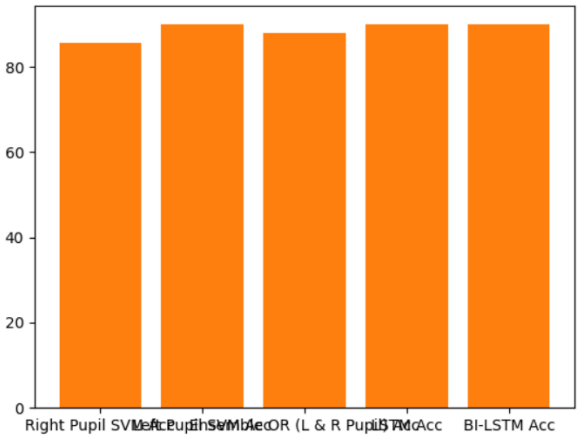


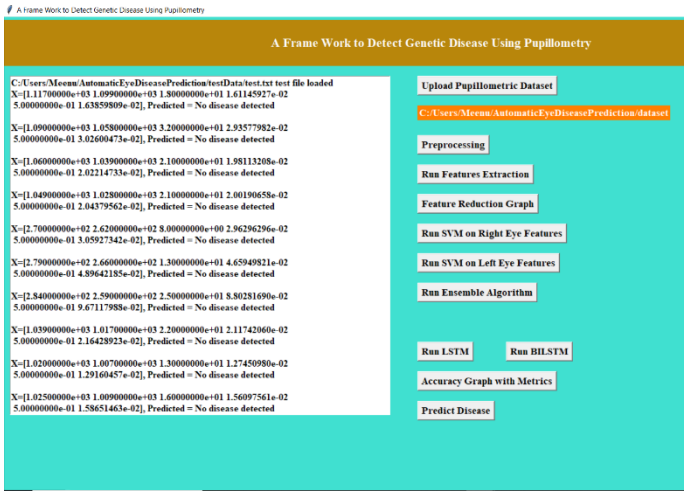
6. RESULT

We obtained the results by giving the image as input in .jpg, .jpeg format to the model.









7. CONCLUSION

In this study, we introduce an innovative approach to assess the reaction of pupils to chromatic light stimuli in pediatric individuals. Our aim is to provide a foundation for clinical decision support in diagnosing retinitis pigmentosa. We developed a robust system based on machine learning (ML) techniques to effectively address artefacts, extract relevant features, and support the diagnosis of retinitis pigmentosa (RP). Our approach utilized an ensemble model comprising two meticulously calibrated support vector machines (SVMs).

Through leave-one-out cross-validation, we evaluated the individual performances of the left and right eyes, enabling us to optimize the internal parameters of the SVMs. The class assignment for each eye was combined using an OR-like method, maximizing the

overall sensitivity of the Clinical Decision Support System (CDSS).

While the ensemble system performed well with the available data, it is crucial to validate its performance on a larger dataset through further testing. Our future plans include conducting comparative analyses with different devices, enhancing the system's versatility.

Notably, the evaluation results demonstrate a specificity of 86%, sensitivity of 90%, and an overall accuracy of 84.6%.

8. REFERENCES

1. X.-F. Huang, F. Huang, K.-C. Wu, J. Wu, J. Chen, C.-P. Pang, F. Lu, J. Qu, and Z.-B. Jin, ‘‘Genotype–phenotype correlation and mutation spectrum in a large cohort of patients with inherited retinal dystrophy revealed by next-generation sequencing,’’
2. R. Kardon, S. C. Anderson, T. G. Damarjian, E. M. Grace, E. Stone, and A. Kawasaki, ‘‘Chromatic pupil responses. Preferential activation of the melanopsin-mediated versus outer photoreceptor-mediated pupil light reflex,’’
3. J. C. Park, A. L. Moura, A. S. Raza, D. W. Rhee, R. H. Kardon, and D. C. Hood, ‘‘Toward a clinical protocol for assessing rod, cone, and melanopsin contributions to the human pupil response,’’ Invest. Ophthal- mol. Vis. Sci., vol. 52, no. 9, pp. 6624–6635, Aug. 2011.
4. A. Kawasaki, S. V. Crippa, R. Kardon, L. Leon, and C. Hamel, ‘‘Char- acterization of pupil responses to blue and red light stimuli in autosomal dominant retinitis pigmentosa due to NR2E3 mutation,’’ Investigative Ophthalmol. Vis. Sci., vol. 53, no. 9, pp. 5562–5569, 2012.
5. A. Kawasaki, F. L. Munier, L. Leon, and R. H. Kardon, ‘‘Pupillometric quantification of residual rod and cone activity in Leber congenital amaurosis,’’ Arch. Ophthalmol., vol. 130, no. 6, pp. 798–800, Jun. 2012.
6. A. Kawasaki, S. Collomb, L. Léon, and M. Münch, ‘‘Pupil responses derived from outer and inner retinal photoreception are normal in patients with hereditary optic neuropathy,’’ Exp. Eye Res., vol. 120, pp. 161–166, Mar. 2014.
7. P. Melillo, A. de Benedictis, E. Villani, M. C. Ferraro, E. Iadanza, M. Gherardelli, F. Testa, S. Banfi, P. Nucci, and F. Simonelli, ‘‘Toward a novel medical device based on chromatic pupillometry for screening and monitoring of inherited ocular disease: A pilot study,’’ in Proc. IFMBE, vol. 68, 2019, pp. 387–390.