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Rationale and protocol paper for the Asia Pacific Network for inherited eye diseases

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ABSTRACT

Purpose: There are major gaps in our knowledge of hereditary ocular conditions in the Asia-Pacific population, which comprises approximately 60% of the world's population. Therefore, a concerted regional effort is urgently needed to close this critical knowledge gap and apply precision medicine technology to improve the quality of lives of these patients in the Asia-Pacific region.
Design: Multi-national, multi-center collaborative network.
Methods: The Research Standing Committee of the Asia-Pacific Academy of Ophthalmology and the Asia-Pacific Society of Eye Genetics fostered this research collaboration, which brings together renowned institutions and experts for inherited eye diseases in the Asia-Pacific region. The immediate priority of the network will be inherited retinal diseases (IRDs), where there is a lack of detailed characterization of these conditions and in the number of established registries.
Results: The network comprises 55 members from 35 centers, spanning 12 countries and regions, including Australia, China, India, Indonesia, Japan, South Korea, Malaysia, Nepal, Philippines, Singapore, Taiwan, and Thailand. The steering committee comprises ophthalmologists with experience in consortia for eye diseases in the Asia-Pacific region, leading ophthalmologists and vision scientists in the field of IRDs internationally, and ophthalmic geneticists.
Conclusions: The Asia Pacific Inherited Eye Disease (APIED) network aims to (1) improve genotyping capabilities and expertise to increase early and accurate genetic diagnosis of IRDs, (2) harmonise deep phenotyping practices and utilization of ontological terms, and (3) establish high-quality, multi-user, federated disease registries that will facilitate patient care, genetic counseling, and research of IRDs regionally and internationally.

The need for an Asia Pacific network for inherited eye diseases

Inherited eye diseases are a leading cause of visual impairment and blindness in children and young working-age adults.[1–3] A diverse array of over 1000 rare inherited eye diseases have been identified on Orphanet; the majority of which have a genetic basis.[4,5] The definition for rare diseases varies from country/region to country/region. Rare inherited retinal diseases (IRDs), defined in Europe as affecting fewer than 5 in 10,000 individuals, tend to be "orphaned" by pharmaceutical companies because of the enormous costs and high risks involved in developing drugs for a small potential market.[6] Even in this age of modern medicine, the vast majority of visually debilitating IRDs continue to lack effective treatments. Individually, IRDs may be rare, but collectively the unmet medical and social needs over a lifetime for affected patients and their families impose a staggering socio-economic burden.[7–10]

In recent years, the pipeline of therapies for patients with IRDs has expanded with advances in basic, clinical, and translational scientific researches, heightened regulatory prioritisation, and increased biopharmaceutical industry investment.[11,12] An unprecedented therapeutic milestone was achieved for IRDs with the approval of Luxturna® (voretigene neparvovec-rzyl) by the United States Food and Drug Administration in 2017, for gene augmentation of biallelic *RPE65* mutation-associated retinal dystrophy.[13] With numerous gene-specific strategies (e.g., gene knockdown and replacement for dominant disease, antisense oligonucleotide therapy, and genome editing using CRISPR/Cas9), gene-agnostic approaches (e.g., optogenetics, small molecule therapy, anti-apoptotic agents, anti-inflammatory agents, anti-oxidative stress agents) and cell replacement (e.g., stem cell transplantation in

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various stages of development), it is anticipated that a growing number of novel therapies will become accessible for IRDs.[14–18]

Between countries in Europe, America, and the Asia-Pacific (APAC) regions, there is notable disparity in rare disease pathways, as well as genetic testings and researches for IRDs.[12] In Europe, there are established national flagship programs for genotyping in Belgium, Czech Republic, France, Latvia, Lithuania, Spain, and the United Kingdom; in the United States, under financing schemes by the Foundation Fighting Blindness and Spark Therapeutics, individuals with a clinical diagnosis of IRD can undergo free genetic testing and counseling.[4] Over the past decade, research on IRDs has been comprehensively performed in European countries and North America, where the majority of IRD-specific therapeutic trials have been conducted.[15,19–21] Considering that the Asia and Pacific regions are home to approximately 60% of the world's population, there is a relative lack of data and clinical trials for IRDs in this population.[12,22,23] Numerous and diverse hurdles need to be overcome to enable universal diagnosis and facilitate the translation of treatments for IRDs effectively and equitably in the APAC region, where different countries are at various stages of economic transformation with varying levels of resources for healthcare services.[23]

The establishment of the Asia-Pacific Inherited Eye Disease (APIED) Network aims to facilitate a concerted regional effort in (I) identifying and overcoming barriers that may hinder the translation of basic science discoveries into clinical care, and (II) coordinating and harmonizing care and research of IRDs regionally and internationally.

Vision and mission of the APIED network

The vision of the APIED network is to herald an era of precision medicine for patients with inherited eye diseases in the Asia-Pacific region.

Our mission is to foster effective and synergistic collaboration to: (I) improve genotyping capabilities and expertise, (II) harmonize phenotyping standards, and (III) establish high-quality data registries, for patients with IRDs in APAC.

Current challenges in the landscape of inherited retinal diseases and strategic focus areas for the APIED network

These pivotal challenges have been preliminarily identified through discussions within the expertize of the steering committee. This committee comprises key opinion leaders (C.P, C.Y, B.L, M.M, M.S and G.K) who are affiliated with established IRD networks in other geographical regions, such as the European Reference Network dedicated to Rare Eye Disease (ERN-EYE, Europe), Foundation Fighting Blindness (FFB, America), and genetic consortia. Our newly established network aims to proactively harmonize our approach in the strategic IRD focus areas outlined in the following section.

Lack of early and accurate genetic diagnosis

Elucidation of the genetic cause of IRDs is important for several reasons. At an individual and family level, this forms the cornerstone for psychological closure, life-planning and reproductive decision-making.[24] From a therapeutic perspective, unraveling the molecular pathomechanism is key to uncovering actionable therapeutic targets and implementing personalized medical care.[25] From a broader perspective, this provides the basis for mapping the genetic landscape of IRDs in APAC and discovering Asian-centric genes and variants.

Genetic testing is a critical step to obtaining a definitive diagnosis due to considerable phenotypic overlap amongst certain IRDs.[26,27] The inception of next-generation sequencing (NGS) technology permitting high-throughput analysis of genomic DNA, and complementary technologies (e.g., transcriptomics, metabolomics, proteomics, and methyl profiling), offer powerful strategies to shorten the diagnostic odyssey for IRD patients.[28,29] Of note, even with NGS techniques, a genetic diagnosis might not be established in 26–48% of individuals;[30] with the bioinformatic pipeline implicated as one of the major sources for variability in variant detection.[31]

Several technical and practical hurdles limit the widespread integration of genetic testing in the management of patients with IRDs in APAC: affordability and funding of investigations; adequate numbers of qualified healthcare professionals to perform genetic counseling and interpretation of results; acceptance by patients from diverse cultural and religious backgrounds; and accessibility of genetic testing facilities and bioinformatic tools.[32] Comprehensively addressing these constraints requires a multifaceted approach that engages regulatory bodies, healthcare systems, clinical laboratories and charitable organizations.[12,32]

The APIED network can enable efforts to achieve genetic diagnosis in several ways:

1. Providing a federated platform for responsible data sharing to aid the interpretation of compelling variants of unknown significance (VUS) and genes of unknown significance (GUS).[29] As patients with the same rare IRD can be geographically dispersed, having a regional network can potentially accelerate the process of identifying additional phenotypically similar individuals with the same variant to accurately call the variant and support novel disease-gene associations.[33]
2. Shared expertise and collaborative analysis using distinct bioinformatic pipelines and tools can also help to boost the diagnostic yield in undiagnosed cases. Joint expertise within the network can be used to suggest best practices for enhancing reproducibility in the bioinformatics pipeline to improve the diagnostic yield of genotyping.
3. Organization of educational programs for ophthalmologists who do not specialize in IRDs to elevate the awareness of the need for genetic testing and counseling.

Heterogeneity in deep phenotyping practices and utilization of ontologies

Deep phenotyping, the precise and comprehensive characterization of phenotypic abnormalities of affected individuals, is key to accurate clinical diagnosis and to stratify patients into clinically meaningful subgroups.[33] Ontologies provide standardized vocabulary terms and nomenclature to describe and perform computational analysis of phenotypic abnormalities found in human disease, allowing data to be Findable, Accessible, Interoperable and Reusable (FAIR principles).[34,35] Ontologies and ontological models also enable the transformation of patient data into machine readable digital objects that is extractable and linkable for knowledge discovery. The main challenge at the intersection of biomedical research and clinical practices is the need to balance data accessibility with privacy and security. In this aspect, privacy-preserving methods are being developed and refined to avoid compromising the individual's identity, which is of exceptional importance when it involves sensitive genomic data.[36,37]

The consistent adoption of both deep phenotyping and ontologies is thus a key step for data sharing and harmonization across different data custodians. This is necessary for scalable linkage of multimodal clinical data with genomic information to train machine learning algorithms that can be used for decision support in determining actionable genetic variants and performing statistical modeling of multi-omics data to identify biological pathways.[38,39] Furthermore, machine readable ontologies can streamline the identification and selection of relevant studies for meta-analysis of various subdomains, and allow 'living reviews' in which published data from new studies can be automatically synthesized to provide constantly updated analyses.[40]

The APIED network can play a role in:

1. Defining minimum standards for deep phenotyping across multimodal investigations to characterize structure and function.

2. Establishing strategic Asian-centric natural history studies, which will provide a powerful tool for understanding the variability in disease onset, degree of severity, and rate of disease progression.[41–43] The identification of critical periods where disease expression and progression occur is requisite to achieve maximal treatment benefit and to guide the selection of the most informative outcome measures in designing clinical trials.
3. Establishing well-characterized molecularly proven patient cohorts for interventional clinical trials.

Lack of high-quality, multi-user IRD disease registries

Disease registries replete with genotypic and phenotypic data can help to overcome numerous research limitations inherent in the study of rare IRDs, such as recruiting an adequate number of patients for clinical trials to avoid underpowered studies. Further, disease registries provide a means for tracking the clinical care and outcomes of IRD patient populations, which is essential for planning health services.[25,26]

The APIED network can play a role in:

- The construction and maintenance of an IRD registry that can be integrated with other databases, such as the European Reference Network dedicated to Rare Eye Diseases (ERN-EYE) to maximize the output of IRD research efforts internationally.[44]

Structure of the APIED network

Steering committee members

The steering committee comprise of ophthalmologists with experience in consortia work for eye diseases in the Asia-Pacific Region (Professor Chi Pui Calvin Pang, Scientific secretary of the Asia-Pacific Society of Eye Genetics; Professor Ching-Yu Cheng, member of the Asian Eye Epidemiology Consortium); leading ophthalmologists in the field of inherited retinal diseases internationally (Professor Bart Leroy, Professor Michel Michelides; and Professor Mandeep Singh) and an ophthalmic geneticist (Professor Govindasamy Kumaramanickavel, Vice-President of the Asia-Pacific Society of Eye Genetics).

APIED network members

Members of the APIED network are nominated through the Asia Pacific Academy of Ophthalmology (APAO) standing Research Committee. Subsequently, additional members are invited to join the network if they are nominated by other IRD specialists, have published population-based studies for IRDs, or are the designated specialists for seeing IRD patients in their institution of practice.

At the time of writing this article, the APIED network has 55 members from 35 centers, spanning 12 countries and regions (Australia, China, Japan, India, Indonesia, South Korea, Malaysia, Nepal, Philippines, Singapore, Taiwan, and Thailand). Table 1. The network also includes executive committee members from the East Asia Inherited Retinal Disease Society (Professor Fujinami Kaoru, President; Professor Woo Se Joon, Vice-President; and Professor Sui Ruifang, Vice-President).

Focused disease areas

The APIED network has several focused disease areas (Fig. 1). The main priorities identified at present are retina, glaucoma, cornea, and ocular malignancies, with the potential to add other disease focus groups in the future. The workgroups that span the different focused disease areas are designed to achieve the key goals of the APIED network. The immediate priority of the network will be on IRDs where paucity in the characterization of these conditions and in the number of established registries remain despite the rapidly evolving therapeutic landscape.

APIED network meetings

The inaugural meeting for the APIED network was conducted in February 2023, at the Asia-Pacific Academy of Ophthalmology (APAO) meeting in Kuala Lumpur, Malaysia. Future in-person meetings are planned to be conducted twice a year: at the annual APAO meeting and the annual Asia-Pacific Vitreo-retina Society (APVRS) meeting. Interval meetings, conducted virtually, will be organized to update network members the status of current collaborations and discuss future collaborations.

Conclusions

The immediate priorities of the APIED network are to delineate the existing practice patterns for IRDs and understand the extent and causes for disparities in data registry, genotyping, and phenotyping practices in the Asia-Pacific region. These insights will serve as a foundation for strategic planning within specialized workgroups, aimed at overcoming challenges and achieving regional harmonization in IRD management.

In the Asia-Pacific region, there exists a significant knowledge gap regarding IRDs. There is a pressing need to close this critical knowledge gap in this era of precision medicine. The APIED network represents a critical first step to enable meaningful collaborations between IRD specialists. This collaborative effort will substantially enhance our efforts in elucidating the clinical and molecular genetic landscape of IRDs, thereby better positioning patients in the Asia-Pacific region to benefit from emerging therapies.

Table 1
Collaborating healthcare institutions in the Asia Pacific Inherited Eye Disease Network.

Country/region	Healthcare Institution
Australia	Lions Eye Institute
	Sir Charles Gairdner Hospital
	Sydney Eye Hospital
	University of Melbourne
China	Beijing Tongren Hospital
	Eye & ENT Hospital of Fudan University
	Joint Shantou International Eye Center
	Peking Union Medical College Hospital
	Peking University Eye Center
	The Chinese University of Hong Kong
	Xiang'an Hospital of Xiamen University
India	Sankara Nethralaya
	Narayana Nethralaya
Indonesia	Dr. Sardjito General Hospital
	JEC Eye Hospitals and Clinics
Japan	Kyoto University Hospital
	National Institute of Sensory Organs, National Hospital Organisation, Tokyo Medical Center
Korea	Seoul National University Bundang Hospital
	Samsung Medical Center
Malaysia	Hospital Canselor Tuanku Muhriz
	Hospital Selayang
	OasisEye Specialists
	UKM Specialist Children's Hospital
	UM Eye Research Centre
Nepal	Tilganga Institute of Ophthalmology
Philippines	Makati Medical Center
Singapore	Eye and Retina Surgeons
	Singapore National Eye Center
	Tan Tock Seng Hospital
	National University Hospital
Taiwan	Cathay General Hospital
	Chang Gung Memorial Hospital
	National Taiwan University Hospital
Thailand	King Chulalongkorn Memorial Hospital
	Ramathibodi Hospital, Mahidol University

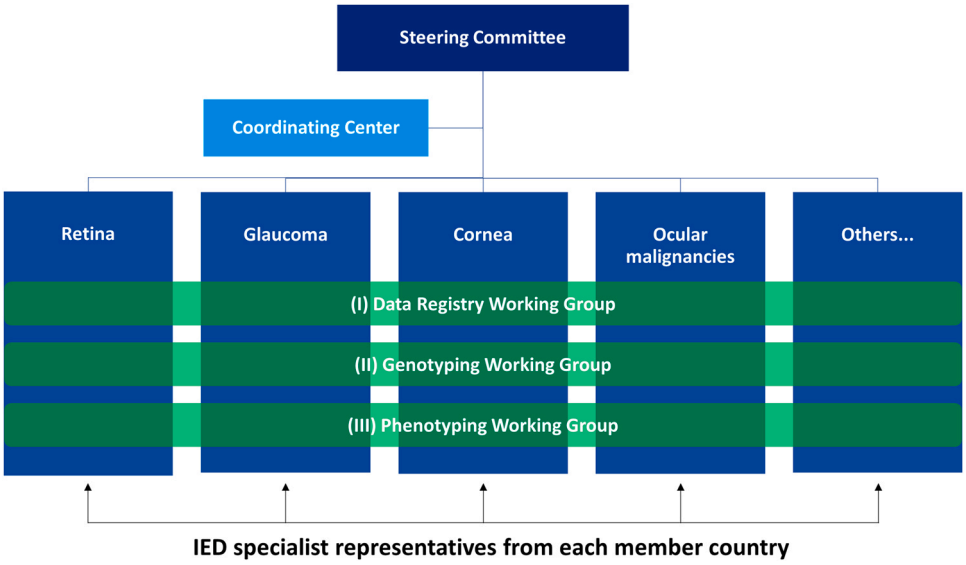

Fig. 1. Organizational framework of the Asia Pacific Inherited Eye Disease Network. The steering committee provides guidance to the various disease focus groups. The pivotal workgroups transcend all disease areas, and is formed by specialists from diverse countries.

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Declaration of Competing Interest

The authors have no conflicts of interest to disclose.

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