Title: Ophthalmic Genetic Counseling: Emerging Trends in Practice Perspectives in Asia

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Abstract

Genetic counselling (GC) provides information to the patient and the family to make informed choices. Amongst the advanced Western countries and a few Asian countries, there are certified or trained professionals who perform GC. The Human Genome Project and next-generation sequencing diagnostics have provided an opportunity for increased genetic testing in the field of ophthalmology. The recent interventional therapeutic research strategies have also generated additional interest to seek GC globally, including in Asia.

However, GC has several barriers to practice in the developing countries in Asia, namely, (a) shortage of qualified or trained genetic counsellors, (b) poor knowledge and reluctance in clinical adoption of genomics amongst the physicians in clinical practice, (c) overstretched public health services and (d), negligible ophthalmic GC related research and publications. The GC inadequacy in Asia is glaring in the most populous countries like China and India, which each have a population of more than a billion inhabitants. Cultural differences, religious beliefs, misogyny, genetic discrimination, and a multitude of languages in Asia create unique challenges that counsellors in the West may only encounter with the immigrant minorities. Since there are currently 500 or more specific Mendelian genetic eye disorders, it is important for genetic counsellors to translate the genetic results at a level that the patient and family understand. There is therefore a need for governmental and healthcare organizations to train genetic counsellors in Asia and especially this practice must be included in the routine comprehensive ophthalmic care practice.

Keywords: Comprehensive ophthalmic care, ophthalmic genetic counselling, mendelian diseases, ophthalmic genetic disorders, direct-to-consumer genetic testing (DTC), next-generation sequencing

What is known about this topic?

Regarding ophthalmic genetic counselling, not much is published in world literature, though the field is widely practiced for couple of decades in many Western and few Asian countries.

What does this paper add to the topic?

There is a dearth of knowledge due to the lack of publications in ophthalmic genetics in global literature. Hence, this paper introduces ophthalmic genetic counselling and the practical challenges related to the discipline in countries in the region of Asia.

Introduction

Medical and clinical geneticists or counsellors provide genetic counselling to educate the patient and family on inheritance, genetic testing, management, prevention, medical and psychological implications of the disease (Resta *et al.*, 2006). They also discuss the educational, employment and social impact of the disease and `refer them to the appropriate rehabilitation and support groups (Resta *et al.*, 2006; Biesecker, 2001; Zhong, Darren and Dimaras, 2017). GC ensures that the patient and family make informed choices (Resta *et al.*, 2006; Revel, 1995; *American Board of Human Genetics*, 2005). Counsellors also give psychological and emotional support and reduce anxiety to the family members (The New York-Mid-Atlantic Consortium for and Newborn Screening, 2009).

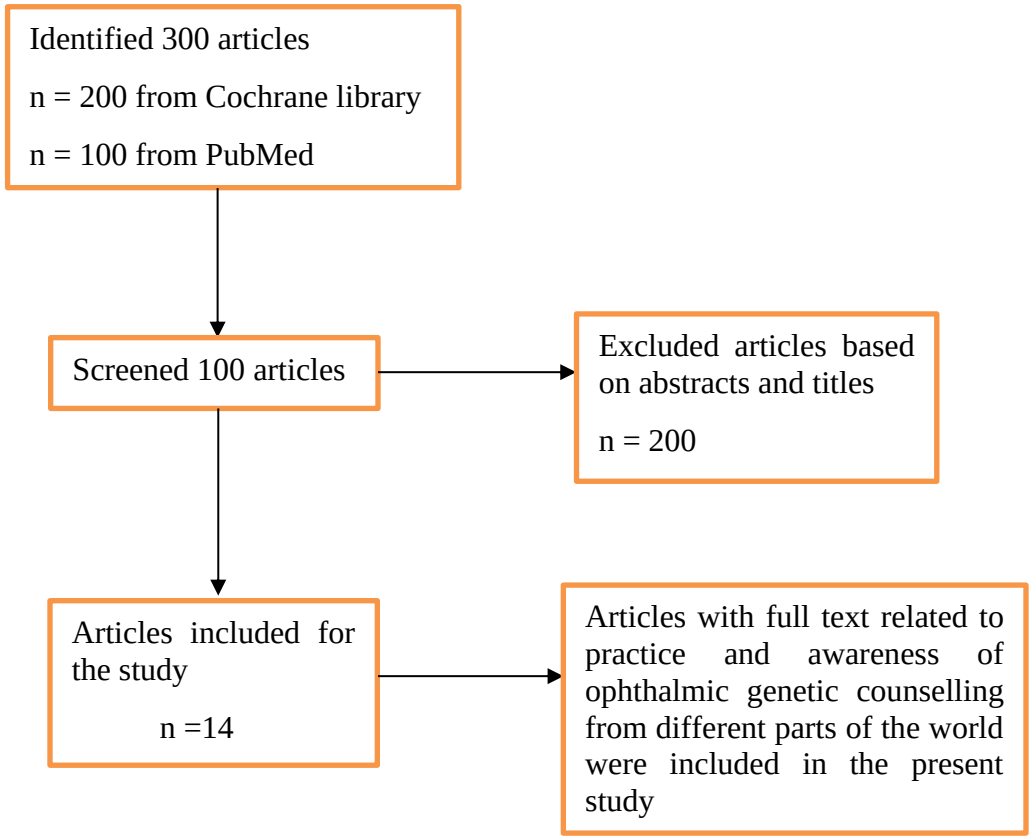
Through the implementation of the Human Genome Project (Chai, 2008), the HapMap Project ('The International HapMap Project,' 2003), and next-generation sequencing (NGS) technology, the ability to make a genetics-based precise molecular diagnosis is now available in all medical disciplines, including ophthalmology. The Mendelian genes in ophthalmology are estimated to have significantly increased to over 500, and among them, one of the largest categories is inherited retinal degenerations (IRDs), with more than 250 genes regulating the retinal histology, physiology and biochemistry (Branham and Yashar, 2013; *RetNet, Retinal Information Network*). Most frequently encountered IRDs in clinical practice, include retinitis pigmentosa (RP) (Hamel, 2006), Stargardt disease (SD) (Hamel, 2007), cone dystrophies (Hamel, 2007), and Leber congenital amaurosis (Ahmed and Loewenstein, 2008), which may all eventually lead to legal or total blindness (Stone *et al.*, 2012). However, the knowledge and skill are deficient amongst the medical professionals in ophthalmic genetics, and this has to be addressed to help the

patient (Wang, 1998; Messner *et al.*, 2016). Even in advanced countries, there is a shortage of genetic counsellors in tertiary hospitals due to a variety of reasons, leave alone Asia (Cohen and Tucker, 2018). Similarly in the West, during comprehensive vision care, inherited eye diseases which lead to visual impairment or blindness require life-long management and continuous support, but the genetic implications are not communicated adequately (Branham and Yashar, 2013; Blain and Brooks, 2007). Available literature has focused on the outcomes of genetic advances or general GC with less emphasis on the subspecialty of ophthalmic GC (OGC).

The focus of this article is on OGC, particularly on the Asian aspects, analysing the genetic counselling challenges (consanguinity, cultural, religious, languages, socio-economic, variants of unknown sequence), and the opportunities (genetic counselling in the next-generation sequencing era). This paper, to the best of our knowledge, is the first to address the unique aspects of OGC in Asia.

Method for systematic review

A literature search was performed in the PubMed and Cochrane Library Electronic Databases. For the search strategy, "OGC", "practice of OGC", and "awareness of OGC" terms were used. After identifying 300 articles which were related to various ophthalmic and other genetic diseases and genetic counselling, we found 14 articles which were only related to ophthalmic genetic counselling from different parts of the world. We could not find publications from Asia. Hence, we selected these 14 articles for the present study. Flowchart for selection of the articles is given below –



14 articles were specific on OGC, but none of them focused on OGC in Asia.(Jay and Evans, 1996), (Macarov *et al.*, 2021), (Stone *et al.*, 2012; Sutherland and Day, 2009).

Genetic Counselling Challenges in Asia

Across the globe health professionals, including geneticists, genetic counsellors, nurses, and physician specialists in the fields of ophthalmology, pediatrics, obstetrics, and gynecology, provide GC. In North America and Australia, GC has been established since the 1950s (Organization; *Genomics*, Nov 2020), and counsellors are certified through the American Board of Genetic Counseling (Bertolini *et al.*, 1993) and the Genetic Counseling Training and Accreditation agency ('National Society of Genetic Counselors,' 1979; McEwen, Young and Wake, 2013), respectively. Counsellors in the West enter the field from a variety of disciplines, such as biology, and nursing, and have specialized graduate degrees in medical genetics or the genetic counseling (Bertolini *et*

al., 1993). A detailed genetic healthcare services workforce information is provided by the United States of America Government (*Information on Genetic Counselor and Medical Geneticist Workforces* July 2020). Besides, most countries in the West (Canada, many European countries, Israel, New Zealand, South Africa, United Kingdom) and few in Asia (Japan, Philippines, Saudi Arabia, Malaysia, South Korea and Taiwan) have a structured GC certified courses (Abacan *et al.*, 2019a; McEwen, Young and Wake, 2013).

Unlike western countries, GC in Asia is a recently emerging clinical trend. The Professional Society of Genetic Counselors in Asia was established recently in 2015. Counselling is available in countries and regions such as Hong Kong, India, Indonesia, Japan, Malaysia, Philippines, Singapore, Thailand, Taiwan and Vietnam (*Asia Pacific Society of Human Genetics*, 2006). China has not yet recognized GC as an independent healthcare profession. However, in India the Board of Genetic Counselling of India, a non-governmental organization, conducts certified GC courses (Abacan *et al.*, 2019a). But nevertheless, counsellors come from a variety of backgrounds and occupations without board certifications (Zhong, Darren and Dimaras, 2017). In Hong Kong, for example, in the Department of Health, clinical geneticists, obstetricians specializing in maternal-fetal medicine, registered nurses and oncologists practice GC (*Genetic Counseling Services*, 2006; Abacan *et al.*, 2019a; Chair *et al.*, 2019). In Taiwan, counsellors have professions outside of the medical field, such as teachers and psychologists (Bhat, 2015). Training is usually performed through workshops, however, some bachelor's and/or master programs have been existing or recently been introduced by universities and boards in Asia, including Japan (~230 genetic counsellors and 14 masters training programs [MTPs]), Malaysia ((<10 genetic counsellors and 1 MTP - certified through the Human Genetics Society of Australasia), Philippines (>10

genetic counsellors and 1 MTP), Singapore (10 genetic counsellors), South Korea (12 genetic counsellors, 2 MTPs) and Taiwan (120 genetic counsellors1 MTPs), whereas for the entire Africa, only South Africa has (~20 genetic counselors, 2 MTPs) (Laurino and Padilla, 2013; Suzumori *et al.*, 2015; Bhat, 2015; Abacan *et al.*, 2019a). In India the Medical Council of India recognized superspecialty medical course on medical genetics is available.

Further, challenges of GC in Asia are the inadequate knowledge of genetics among physicians, the absence or shortage of counsellors, limited access to genetic services, and absence of legal regulations on genetic discrimination. Lack of recognition, low professional income, and poor regulatory implementation of genetic counsellors at the ground level are additional challenges in this field. These problems are especially prominent in highly populated countries like India and China. (Zhong, Darren and Dimaras, 2017). Although genetic testing in Thailand was available 30 years ago, there are still only 22 clinical geneticists for 69 million people (Shotelersuk, Limwongse and Mahasirimongkol, 2014). Malaysia has a population of 32 million, but there are only nine medical geneticists and two genetic counsellors. However, the ratio between medical geneticists to the population is one is to 3 million (Zayts *et al.*, 2013), and genetic counsellors to the population is one is to 14 million (Lee and Thong, 2013). In Japan with a population of 126 million, only 151 genetic counsellors are available and most of these counsellors work in private infertility clinics, which offer better salaries than tertiary centres, university hospitals or medical centres (Suzumori *et al.*, 2015). With a population of 327 million USA has 4000 board-certified genetic counsellors, whereas in India with a 1.3 billion population there are less than 100 genetic counsellors (Abacan *et al.*, 2019b).

Genetic counselling is important for couples in the regions where discrimination against disabilities are deeply rooted in the society (Kato, 2010; Suzumori *et al.*, 2015). In Asia, there are few or no anti-discrimination laws to protect patients with genetic disorders. Most Western countries have laws against genetic discrimination, including the Genetic Information Non-discrimination Act in the United States ('Genetic Information Nondiscrimination Act. Final rule,' 2016), and the United Nations' International Declaration on Human Genetic Data (United Nations Educational, Scientific and Cultural Organization, 2004). The declaration specifically states that genetic information cannot cause harm to employment, insurance, and other areas. Although this applies to Asian countries by default, it is neither strictly regulated nor enforced by the authorities in countries like Thailand (Shotelersuk, Limwongse and Mahasirimongkol, 2014), and Singapore (Yoshizawa *et al.*, 2014). A company in Guangdong, China went against the Charter of the United Nations on genetic privacy and discrimination as they declined job offers for three applicants with thalassemia. (Sleeboom-Faulkner, 2011; Qiu, 2010). The local district court also rejected the job applicants' first appeal and did not acknowledge the genetic non-discrimination policy. As genetic testing becomes more readily available to the public, there is a pressing need for counselors to educate patients and the public, and to combat genetic discrimination with strictly regulated and enforced national laws.

Moreover, genetic counsellors in Asia face challenges in religion, culture, and language as well. Building on Zayt et al., study (Zayts *et al.*, 2013), research counsellors must be competent in addressing challenges in a geographical cultural environment (Weil and Mittman, 1993; Warren, 2011), and in understanding ethnocultural groups' social behaviours. India and China, the countries with the largest populations in Asia, have a mixture of various ethnic and cultural groups.

Counsellors must be sensitive in Asia because of the cultural practices in these countries that influence the decision-making process.

Genetic Counselling Challenges in India

Asian Indians are physically, culturally, and linguistically a heterogeneous group. In general, Indians in the North and West are tall and fair with Caucasian features, whereas those in the South are short and dark-complexioned with Dravidian origins, but individuals in the East are short and fair complexioned with Sino-Tibetan features. Hindi and allied languages are spoken in the North, whereas allied Dravidian languages in the South.

Genetic counsellors in Asia must be sensitive to religious beliefs, especially for discussions on consanguineous marriages, abortion, birth defects and abnormalities, and the genetic disease's social and financial consequences. Approximately 99% of the population in Thailand is Buddhist (Shotelersuk, Limwongse and Mahasirimongkol, 2014) and 80.5% of the population in India is Hindu. (*Religion* 2011). For these populations, disabilities and genetic disorders are viewed because of *Karma*, taboo, or family curse, which is associated with a strong social stigma and discrimination.

Consanguineous marital practices, with changing trends, are widely prevalent among not only Asian cultures, but also amongst different religions in Asia (Jones, 2010). The inability to marry outside of the family due to a major blinding ophthalmic genetic disorders or other genetic disorders is a common constraint. Prospective exogamous partners refuse to marry even to the unaffected in a family with the disease, hence at times, such families conceal genetic family history

from the prospective partner's family or forced to marry consanguineously. In India, matrimonial prospects are mostly enquired about and arranged by the parents and extended family members, where the prospective groom and brides' opinions are of least priority (Zhong, Darren and Dimaras, 2017). Despite our counselling, a few families married consanguineously, as a result, their newborns had inherited the blinding ophthalmic genetic disorders in an autosomal recessive manner (pseudo-dominance). Catholicism forbids consanguineous marriages, however in the State of Tamil Nadu, India, Catholics write to the Pope and get special permission for consanguineous marriages to be solemnized in their local Church, which is showing that consanguinity is a cultural practice rather than a religious practice.

Previous studies of IRD in India indicate that over 50% of RP were transmitted in an autosomal recessive mode due to consanguineous marital practices (Bhat, 2015; Kumaramanickavel *et al.*, 2002). To prevent genetic disorders, some Asian countries, such as Taiwan, established a law against consanguineous marriages in 1985 (Chien, Su and Chen, 2013). This phenomenon calls for additional counsellors to educate and create awareness among the families and the public on the inheritance of autosomal recessive disorders. (Akrami, 2012).

Language Challenges in Asia

In Hong Kong, most of the population speaks Cantonese (89.5%), but Mandarin (1.38%), other Chinese dialects (4.02%), English (3.5%) and other languages (1.57%) are also spoken (*Official Languages Division*, 2012). In other Southeast Asian countries, such as Malaysia, the population is composed of more than 4 ethnic groups, where the official language Malay, English, Tamil and other local dialects are spoken (Lee and Thong, 2013). The language barrier is even

more complex in India, where there are 22 major languages and 720 dialects spoken. Words such as “gene” and “genetic disorder” are mostly absent in vernacular languages and hence counsellors may take an arduous route to explain such concepts (Bhat, 2015). As a result, in urban centres, GC is usually performed in English or widely spoken language like Hindi. However, in China, most of the population is Han Chinese, with a small population of Tibeto-Burman, and Muslims. Mandarin is spoken predominantly in the North of China and Cantonese in the South.

General Issues in Next Generation Sequencing

NGS has enabled genes of Mendelian diseases to be sequenced at a low cost with a rapid turn-around time (Boland *et al.*, 2015; Ng *et al.*, 2010; Bamshad *et al.*, 2011; Bilguvar *et al.*, 2010). WES allows for molecular diagnoses which can have immediate application to clinicians' diagnostic dilemmas and reduce differential diagnosis ambiguity, particularly in rare and ultrarare disorders (McDonell *et al.*, 2014; Bamshad *et al.*, 2011; Souche *et al.*, 2022). Patients should be informed that one-third of the time, the results of genetic testing may not provide a definitive molecular diagnosis. WES studies also provide knowledge to identify essential pathways in disorders, providing the potential molecular diagnoses needed for diseases with complex

phenotypes (Stitziel, Kiezun and Sunyaev, 2011). In Haack et al.’s study, WES revealed mutations in *ACAD9*, a member of the mitochondrial acyl-CoA dehydrogenase protein family. The identification of the mutation allowed promising daily riboflavin treatment to be developed for patients with this condition (MIM 252010) (Gilissen *et al.*, 2011; Haack *et al.*, 2010).

Variants of unknown sequence (VUS) is the biggest challenge in the NGS era. If a patient consults more than one counsellor, their opinions on VUS may be differing. The limitations of WES, like VUS must be explained during pre-test GC. Genome Aggregation Database (gnomAD) is an useful tool while interpreting VUS (Karczewski *et al.*, 2020). Irrespective of the genetic result being pathogenic, likely pathogenic, benign or VUS, it must be reported and explained to the patient. The growing number of incidental findings calls for a more accurate sequencing approach (Van Der Schoot *et al.*, 2022). The American College of Medical Genetic and Genomics defines incidental findings as "unexpected positive findings [that are] results of a deliberate search for pathogenic or likely pathogenic alterations in genes that are not apparently relevant to a diagnostic indication for which sequencing test was ordered" (Green *et al.*, 2013). WES or clinical exome sequencing could identify pathogenic genes that predisposed individuals to breast or prostate cancers. Some patients have indicated incidental findings to improve their quality of life, while others were unsure due to religious reasons, socioeconomic status, the burden of knowledge and other future repercussions, such as insurance eligibility (Clift *et al.*, 2015). Therefore, a counsellor must be trained and oriented towards the sensitivities of these issues.

During pre-test counselling, patients should be informed of the available healthcare insurance coverages. According to the largest review on genetic policies in the United States, one-third of the insurers had at least one general genetic test policy. Multiple plans recognize other services, such as diagnostic testing, genetic counselling, and prenatal diagnosis (Graf *et al.*, 2013). In contrast, there is no published data on private insurance tests for prominent Asian countries such as China, India, Japan, and Malaysia. The lack of insurance coverage coupled with the rise in direct-to-consumer companies (Graf *et al.*, 2013) mean that individuals will most likely purchase

their own genetic tests without going through a physician, resulting in a higher demand for GC outside of the traditional clinical practice settings.

Genetic Testing for Common Eye Diseases

Counsellors need to be updated with the available and appropriate ocular genetic tests (Lee and Couser, 2016). In RB the penetrance is nearly 100% with truncating variants, but can be lower (<25%) in those with non-truncating pathogenic variants (Lohmann *et al.*, 1996; Sippel *et al.*, 1998; Yam *et al.*, 2017). Those with the *RB1* gene mutations or deletions are at risk for developing osteosarcomas, brain tumours and melanoma, which is to be kept in the mind by the genetic counsellor, while counselling and in India, we mention this to the father and not the mother (Fletcher *et al.*, 2004; Lee and Couser, 2016). Anecdotal experience of us is that the fathers could take the stress and balance their emotions better compared to women, in front of their children while counselling. IRDs are a group of disorders that can cause blindness and affect approximately 1 in 3000 persons (Daiger, Bowne and Sullivan, 2007; Ku and Pennesi, 2015; Lee and Couser, 2016). The costs of genetic tests are becoming uniform and cheaper by the day and WES is used for Stargardt disease (SD) (Battu *et al.*, 2015; Strom *et al.*, 2012). The use of large gene panels and WES has been widely accepted, and the diagnostic yield from different reports has been over 50% (Glocke et al., 2014; Lee et al., 2015; Green et al., 2013).

Challenges of Ocular Genetic Counseling in Asia

In predictive (pre-symptomatic, pre-marital) counselling, experience is observed in performing GC with retinoblastoma (RB) (Amitrano *et al.*, 2015) and RP (Tiwari *et al.*, 2016) families in Asia. In the Bardet-Biedel syndrome (BBS), all five cardinal features of RP, obesity, mental retardation,

hypogonadism, and polydactyly—may or may not manifest. Therefore, it can be challenging to counsel these families regarding future generations. For example, one of our patient families had five children, and four had BBS, and due to the variable expressivity of the gene in everyone, the affected children had two or three non-similar phenotypic clinical features out of the cardinal five. And hence caution should be undertaken by the counsellor while discussing the possible phenotype in preconceptional or prenatal couselling. The counsellor must reveal information to the family with caution during pre-symptomatic GC, particularly if the disease can inevitably lead to blindness. Information revealed due to genetic testing could trigger severe psychological depression and suicidal tendencies and hence sensitivities have to be part of such GC (Paulsen *et al.*, 2005). One of our patients studying in college was diagnosed with RP, and she went into further depression when her genetic test revealed a mutation in a gene causing Usher syndrome, as she got more worried if she may develop hearing loss. Pre-symptomatic genetic counselling is especially important for diseases like RB. In our experience, we screened a 5-day-old infant for the autosomal dominant RB disease allele in the family. It was a relief to the family that the child did not carry the disease allele (Ramprasad *et al.*, 2007). In other cases, it can be fatal if not diagnosed nor clinically managed early (Girardet *et al.*, 2003). Pre-marital screening is increasingly popular in Asia, where more trained, oriented, and experienced genetic counsellors are needed. In our experience, unaffected family members with a history of RP, RB, oculocutaneous albinism, and myopia have sought premarital GC. For instance, patients with oculocutaneous albinism in South India must socially adjust to living in a population with a mostly dark-skinned complexion. A marriage proposal can be rejected because of a genetic report suggesting infertility and hence counsellors in Asia and elsewhere should be aware of these facts while counselling (Greil, Slauson-Blevins and McQuillan, 2010).

OGC is unique because, as mentioned earlier, there is a great degree of overlap among retinopathies with genetic and clinical heterogeneities. For example - the *ABCA4* gene has been associated with Stargardt disease, RP, cone-rod dystrophy, and cone dystrophies (Ku and Pennesi, 2015). The rate or degree of disease progression leading to blindness must also be discussed with clarity (Lee and Couser, 2016). Moreover, these blinding ophthalmic genetic disorders are not lethal and can pose an ethical dilemma when couples seek a counselor's view on abortion. Syndromic and non-syndromic RP has mutations in more than 150 different genes. (Daiger, Bowne and Sullivan, 2007; Chizzolini *et al.*, 2011; Lee and Couser, 2016). RP could be inherited in an autosomal pseudo-dominant manner in highly consanguineous populations, like southern India or in an X-linked recessive mode, where the background consanguinity may be misleading (Fahim AT, Daiger SP and RG, 2000). Isolated affected male or female probands can be another challenge during GC trying to discuss the possibility of next generation being affected. The presence of *de novo* mutations in the family and female carriers exhibiting the phenotype can easily mislead a counsellor; and an X-linked pedigree may appear to be autosomal dominant, if there is consanguinity. Hence, genetic counselors must thoroughly ascertain several generations during the pedigree analysis.

The prevalence of myopia in India, however, is much lower compared to the East Asian populations including China, where it could be as high as 70 to 80% of the population (Saxena *et al.*, 2015), (Wong and Saw, 2016). Counselling such families can be challenging because advising someone to restrain from marrying another individual with myopia is controversial and impractical, since it is not a fatal disease. Congenital glaucoma and Peter's anomaly autosomal recessive

conditions are prevalent in consanguineous communities, including India where GC could be useful. The mutation would usually be a compound heterozygote in a non-consanguineous family, unlike in consanguineous families where it would be homozygous. Congenital cataract usually is autosomal dominant, so GC and prenatal diagnosis can be useful for early interventional cataract surgery in infants, before the formative years of vision.

Screening can also be done prenatally using chorionic villus sampling (CVS) or amniocentesis. This knowledge could be overwhelming leading to 'information overload' for patients and families of lower socioeconomic status in Asia (Bartley *et al.*, 2020). There are collective eyecare issues in India, such as the inaccessible and overburdened public healthcare services and on the other hand, exorbitant costs in private healthcare services.

Non-directive counselling has been an approach that genetic counsellors in the West adopted since the 1950s. The approach incorporates psychosocial elements into GC to ensure that the patients make well-informed choices while respecting their autonomy (Chieng, Chan and Lee, 2011). However, the patient's autonomy in Asia is viewed in a collective manner by the family members (Chieng, Chan and Lee, 2011; Zhong, Darren and Dimaras, 2017). The opinion of extended family members, particularly those from the husband's side of the family, influence the decision-making process in these societies. For example, in one of our cases, an infant's diagnosis of RB was delayed because of his paternal grandparents' influence. His mother discovered that the infant had impaired vision at three months of age. She informed her husband, but the in-laws saw the child's condition of visual problems cannot be a punishment from God and ignored the detection of the mother. Six months later, the mother took the child to an ophthalmologist without

the knowledge of the in-laws. The child was diagnosed with RB and one of the eyes was enucleated. Basic medical knowledge is not as commonly known to the public prior to counselling in Asia, and hence may be completely new information to the patients. Non-directed conventional counselling hence may not be the best approach in Asia, especially in India and China (Chieng, Chan and Lee, 2011). In conclusion, Asia holds nearly two thirds of the world's population, though with a variety of challenges, OGC practice should be implemented in comprehensive ophthalmic care, with the help of the private and Governmental sectors, to benefit the Asian communities.

Author's contribution

Esther K.Y. Hui: wrote the manuscript and done referencing
Jason C.S. Yam: guided the manuscript
Farhana Rahman: reviewed and made correction of the manuscript
Chi Pui Pang: overall core support
Govindasamy Kumaramanickavel: overall concept, discussion, and guidance

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