Spectrum of inherited eye disorders at Hong Kong Children's Hospital: insights into the local genetic landscape and experience with ocular genetic services

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ABSTRACT

Introduction: Inherited eye disorders (IEDs) are a leading cause of visual impairment. However, local data and information about the genetic landscape of IEDs in Hong Kong remain limited. This study aimed to examine the diagnostic yield, mutational spectrum, and clinical utility of genomic testing in patients with IEDs at a major local centre.

Methods: This retrospective observational study included 130 patients with suspected IEDs who attended the genetic counselling clinic at the Department of Clinical Genetics of the Hong Kong Children's Hospital between December 2021 and October 2023. Analyses were conducted on the spectrum of ocular genetic disorders, genetic variants, diagnostic yields, and clinical utility of genomic testing.

Results: The overall diagnostic yield of genomic testing was 51.5%. Inherited retinal disorders accounted for approximately 60% of positive results. Patients with syndromic features and a positive family history were significantly more likely to receive a molecular diagnosis (P<0.05). Clinical utility of genomic testing was observed in over 70% of patients with positive results. With genetic counselling, a confirmed molecular diagnosis contributed to disease prognostication, avoided unnecessary investigations, guided clinical management, and facilitated reproductive planning and family cascade screening.

Conclusion: There is a growing demand for the application of genomic medicine in patients with IEDs. Genetic testing is widely accepted and demonstrates high diagnostic and clinical utilities. The multidisciplinary team clinic service model is the global trend for integrating genomic testing into routine care. Hong Kong Children's Hospital is implementing this model to meet the evolving needs of this patient population.

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New knowledge added by this study

- The local diagnostic yield of genomic testing in patients with inherited eye disorder (IED) is 51.5%.
- Molecular confirmation of IEDs in more than 70% of patients demonstrated the clinical utility of genomic testing.

Implications for clinical practice or policy

- Incorporation of genetic testing into routine IED workup is imperative.
- Implementation of a multidisciplinary team or combined clinic model—including ophthalmologists, geneticists, genetic counsellors, optometrists, and nurses—enables personalised and timely management of IED patients.

Introduction

According to World Health Organization estimates, approximately 19 million children under the age of 15 years are visually impaired, with 1.4 million exhibiting irreversible impairment.[1] Among cases of severe visual impairment diagnosed before the age of 1 year, around one-third are attributable to genetic causes.[2]

香港兒童醫院遺傳性眼疾的病譜：深入了解本地遺傳基因特徵與遺傳性眼科服務經驗

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引言：遺傳性眼疾是導致視力受損的重要原因之一。然而，目前香港本地關於此類疾病及其基因特徵的資料仍然有限。本研究旨在探討基因檢測在本地一所主要醫療中心中，對遺傳性眼疾患者的診斷成效、基因變異譜，以及其臨床上的應用價值。

方法：本回顧性觀察研究共納入130名懷疑患有遺傳性眼疾的患者，他們於2021年12月至2023年10月期間，曾在香港兒童醫院醫學遺傳科的遺傳輔導診所就診。研究分析內容包括眼科遺傳病的種類、相關的基因變異、基因檢測診斷率，以及基因檢測在臨床上的應用價值。

結果：基因檢測的整體診斷率為51.5%。在所有陽性結果中，約有60%屬於遺傳性視網膜疾病。具有綜合徵特徵或有家族病史的患者，其獲得分子診斷的機會明顯較高（$P < 0.05$）。超過70%檢測結果呈陽性的患者中，基因檢測顯示有臨床應用價值。透過遺傳輔導，已確定的分子診斷有助預測病情發展、減少不必要的檢查、協助臨床決策，亦有助病人計劃生育及安排家族成員進行相關基因檢測。

結論：遺傳性眼疾患者對基因醫學的需求日益增加。基因檢測已廣泛被接受，並展現出良好的診斷成效及臨床應用價值。採用多專科團隊診所模式已成為全球推動基因檢測納入常規醫療的重要發展方向。香港兒童醫院正逐步推行此項模式，以回應此類患者不斷演變的醫療需求。

Substantial proportions of childhood and adult-onset visual impairments are caused by inherited eye disorders (IEDs), which include anterior segment dysgenesis; inherited retinal disorders (IRDs); microphthalmia, anophthalmia, and coloboma; ocular tumours; congenital cataracts; and albinism. Over the past three decades, more than 450 genes have been associated with IEDs.[2,3] Genetic diagnosis in such cases is challenging due to both clinical and genetic heterogeneity.

Ocular genetics has rapidly evolved over the past decade—from identifying inheritance patterns of IEDs to establishing genotype-phenotype correlations for disease prognostication and enrolling patients in gene therapy trials. In 2018, the United States Food and Drug Administration approved the first ocular gene therapy, Luxturna, for the treatment of *RPE65*-related inherited retinal disease.[4] In 2012, the American Academy of Ophthalmology published diagnostic guidelines encouraging the routine use of genetic testing for IEDs.[5] Multiple genes can now be assessed simultaneously through a single genomic test, which is particularly useful for identifying heterogeneous single-gene disorders and resolving cases where a clinical diagnosis is difficult to establish.[6] Advances in sequencing technologies are uncovering the molecular aetiologies of various disorders. Consequently, the genomic approach to IEDs is gaining popularity, highlighting the need for more sophisticated genomic testing and comprehensive ocular genetic services.

In Hong Kong, the Retinitis Pigmentosa Registry—the first of its kind among Chinese populations globally—was established in 1995. Its main objectives are to provide detailed ophthalmic and genetic examinations for patients with inherited retinal degenerative diseases and to build a database for future scientific, medical, and sociological research.[7] However, local data remain limited and the genetic landscapes of other IEDs are still unclear.

Hong Kong Children's Hospital (HKCH) serves as the tertiary referral centre for complex, serious, and uncommon paediatric cases requiring multidisciplinary management, providing diagnosis, treatment, and rehabilitation services across the territory. In 2021, the Clinical Genetics Service Unit (CGSU) at HKCH was established as the first clinical genetics branch under the Hospital Authority. In July 2023, the Clinical Genetic Service (CGS) of the Department of Health (DH)—the former government-funded tertiary genetic referral centre providing genetic counselling and laboratory services to the entire Hong Kong population—was integrated with the CGSU and renamed the Department of Clinical Genetics (DCG) under the Hospital Authority. As a major clinical genetics service provider in Hong Kong, the DCG now offers genetic counselling services territory-wide.

Acknowledging the knowledge gap in the local genetic landscape and the lack of a comprehensive service model for patients with IEDs in Hong Kong, we conducted this retrospective review to analyse the local mutational spectrum across various IED subtypes and the corresponding diagnostic yield in our institution. Our aim was to better understand the clinical utility of genomic testing in IED patients and to formulate a comprehensive ocular genetic service model that addresses the needs of local patients.

Methods

Study design and population

Patients presenting with eye manifestations were retrospectively identified by querying records between 1 December 2021 and 30 October 2023 through the Hospital Authority Teams database under the CGSU/DCG at HKCH. The database included all patients who had attended genetic counselling clinics under the CGSU/DCG. Clinical geneticists and ophthalmologists reviewed all clinical notes, genetic reports, and electronic health records in the Clinical Management System, as well as paper records.

Patients' phenotypes were reviewed and categorised by ophthalmologists into the following nine groups: (a) anterior segment dysgenesis;

(b) IRDs; (c) cataract and lens disorders; (d) microphthalmia, anophthalmia, and coloboma spectrum; (e) neuro-ophthalmology (eg, optic atrophy); (f) ocular albinism or oculocutaneous albinism; (g) high myopia; (h) ocular tumours; and (i) others.

Patients with inconclusive eye phenotypes were excluded. Relevant history (including consanguinity, ethnicity, and family history), physical examination findings (dysmorphism and involvement of other systems), ophthalmological assessments and examinations, other relevant investigations (eg, magnetic resonance imaging of the brain and renal imaging), and previous genetic test reports were reviewed. A positive family history was defined as the presence of related eye phenotypes in a first-degree relative, or in two or more second- or third-degree relatives with the same condition.

All patients underwent comprehensive dysmorphology evaluations and genetic counselling, including pre-test and post-test consultations with the clinical genetics team. Prior to providing informed consent for genomic testing, patients were counselled on the indications, limitations, diagnostic yield, variants of uncertain clinical significance, and the ethical, social, and legal implications of genomic testing. Informed consent was obtained from affected patients or their legal guardians before undergoing diagnostic genomic testing.

Genomic testing

According to clinical indications, patients were offered various genomic tests, including single-gene sequencing, array comparative genomic hybridisation, multiplex ligation–dependent probe amplification, whole-exome sequencing–based panels, medical exome sequencing, and mitochondrial sequencing. DNA was extracted from peripheral blood ethylenediaminetetraacetic acid samples. For mitochondrial sequencing, mitochondrial DNA extracted from urine-derived cells was used. All tests were performed in one of two accredited laboratories: the Genetic Laboratory of DH (which became a combined service with the Hospital Authority after July 2023), or the Genetics and Genomics Laboratory at HKCH, in accordance with laboratory-specific protocols and guidelines. Inheritance and phasing were determined via targeted Sanger sequencing of parental samples.

Data collection and analysis

Clinical characteristics were collected from electronic records and, when available, hospital case notes and CGS paper records. These characteristics included age at onset, age at first encounter, sex, ethnicity, consanguinity, laterality of ocular involvement, severity of visual impairment, family history of ocular conditions, syndromic features, and other associated system involvement. Genetic testing results were retrieved from the Clinical Management System, CGS database, and paper records. Additionally, reproductive planning (for either the index patient or their parents) and other subspecialty referrals after a substantiated molecular diagnosis—as documented in genetic counselling notes—were recorded for clinical utility analysis. All clinical data are presented as percentages or means ± standard deviations, unless otherwise specified.

Molecular and clinical data from all recruited individuals were analysed using SPSS (Windows version 26.0; IBM Corp, Armonk [NY], United States). Categorical variables (eg, syndromic vs non-syndromic presentation, presence of family history) were compared using Fisher's exact test, while continuous variables were compared using the independent samples *t* test. P values of less than 0.05 were considered statistically significant. This article was written in compliance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines.

Results

Between December 2021 and October 2023, 3653 patients were registered at the HKCH genetic counselling clinic. Of these, 148 symptomatic patients from 147 families met the inclusion criteria for this study. Approximately 4% of patients presented to the genetics clinic with ophthalmological diseases. Overall, 130 (87.8%) patients consented to genomic testing (Fig).

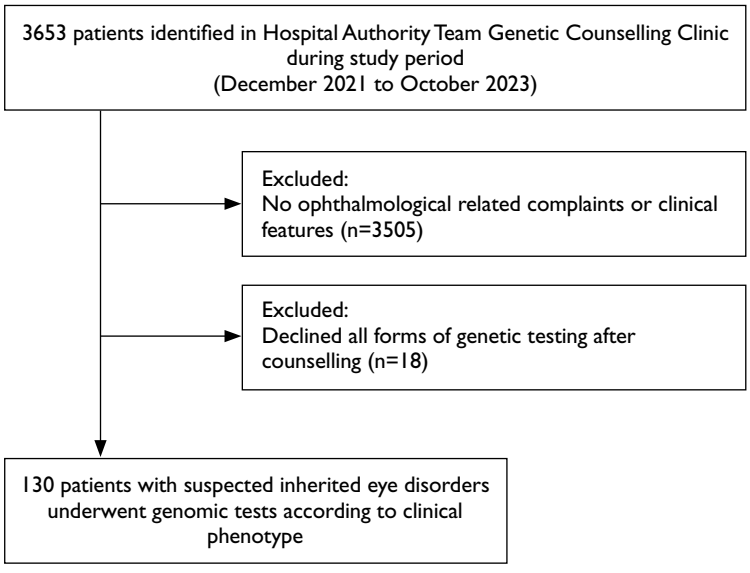

FIG. Patient selection for analysis

Patient demographics

Among the 130 patients, approximately 92% were Chinese, with a male-to-female ratio of 3:2. The mean age (±standard deviation) at onset was 12.5±16.2 years. Within this cohort, 53.1% of patients were classified under IRDs, 14.6% under neuro-ophthalmology, and 13.8% under cataract/lens disorders.

Fifteen patients (11.5% of those tested) presented with more than one ocular phenotype. The majority of patients (>80%) exhibited bilateral ocular involvement. Detailed demographics, family history, and disease categories of the 130 patients who underwent genetic testing are presented in Table 1.

TABLE 1. Patient demographics (n=130) and disease categories*

	Value
Sex	
Male	77 (59.2%)
Female	53 (40.8%)
Ethnicity	
Chinese	120 (92.3%)
Non-Chinese	10 (7.7%)
Family history of eye disorders	
Yes	41 (31.5%)
No	89 (68.5%)
Age at first encounter, y	
Mean ± SD	21.9 ± 20.9
Median (range)	14.0 (0.0-72.0)
Age at onset, y	
Mean ± SD	12.5 ± 16.2
Median (range)	4.5 (0.0-68.0)
Duration between onset and first encounter, y	
Mean ± SD	10.0 ± 11.4
Median (range)	5.8 (0.0-48.0)
Disease category	
Anterior segment dysgenesis	6 (4.6%)
Inherited retinal disorders	69 (53.1%)
Cataract/lens disorders	18 (13.8%)
MAC spectrum	5 (3.8%)
Neuro-ophthalmology	19 (14.6%)
OA/OCA	4 (3.1%)
Ocular tumours	17 (13.1%)
High myopia	9 (6.9%)
Others	2 (1.5%)
More than one category	15 (11.5%)
Ocular involvement	
Bilateral	113 (86.9%)
Unilateral	17 (13.1%)

Abbreviations: MAC = microphthalmia, anophthalmia, and coloboma; OA = ocular albinism; OCA = oculocutaneous albinism; SD = standard deviation

* Data are shown as No. (%), unless otherwise specified

Molecular findings and diagnostic yield

The diagnostic yield of genomic testing was defined as the proportion of individuals with pathogenic or likely pathogenic molecular variants or structural variants contributing to the clinical phenotype. A whole-exome sequencing–based virtual panel was requested for 78 (60%) of the 130 patients, based on their presenting phenotypes (online supplementary Table 1). Using this panel-based approach, the diagnostic yield was 51.3%. Twenty-three patients (17.7%) underwent single-gene testing based on highly specific phenotypes without molecular heterogeneity, such as *RB1*, *CHD7*, *NF1*, and *RS1* (online supplementary Table 2). This single-gene approach successfully diagnosed 14 patients (60.8%). Medical exome sequencing was offered to 22 patients with multiple congenital anomalies or suspected syndromes, achieving a diagnostic yield of 50% (11/22). Two patients were diagnosed through copy number variation analysis (online supplementary Table 2).

The overall diagnostic yield for this cohort was 51.5% (Table 2). As mentioned earlier, 15 patients exhibited overlapping phenotypes across disease categories, with inherited retinal disorders and cataracts being the most common co-existing phenotypes. The microphthalmia, anophthalmia, and coloboma spectrum demonstrated the highest diagnostic yield at 100%. All five patients in this category presented with bilateral eye involvement and were syndromic (eg, two with CHARGE syndrome) [online supplementary Table 2]. Among the 69 IRD patients who underwent testing, 40 had confirmed molecular diagnoses, resulting in diagnostic yield of 58% for the IRD group. The most commonly identified genes were *USH2A*, *ABCA4*, *COL2A1*, *RP1L1*, and *RS1* (online supplementary Table 2). No significant differences in diagnostic yield were detected across disease categories (Table 2).

Patients presenting with IRDs and neuro-ophthalmological conditions generally exhibited a later age at onset and age at first encounter compared with other categories, although these differences were not statistically significant (Table 2).

In total, 25 novel variants were identified in 25 patients across 20 genes. Of these, four remained of uncertain clinical significance despite further phasing and segregation analysis (online supplementary Table 2). Five variants were found in trans with another likely pathogenic variant in the same gene,

TABLE 2. Diagnostic characteristics of genetic testing by disease category

Disease category	No. of patients tested	Age at onset, y		Age at first genetics clinic visit, y		No. of confirmed diagnoses	Diagnostic yield (%)†	P value‡
		Mean ± SD	Median (range)	Mean ± SD	Median (range)			
Anterior segment dysgenesis	6	4.5 ± 11.0	0.1 (0.0-27.0)	9.5 ± 9.5	9.0 (0.6-27.0)	3	50.0	1.00
Inherited retinal disorders	69	16.4 ± 17.3	13.0 (0.4-60.0)	26.9 ± 21.8	18.0 (0.5-72.0)	40	58.0	0.19
Cataract/lens disorders	18	5.7 ± 14.0	1.5 (0.0-58.0)	12.2 ± 16.6	7.0 (0.0-68.0)	12	66.7	0.21
MAC spectrum	5	19.3 ± 33.5	0.0 (0.0-58.0)	17.6 ± 28.8	3.5 (0.5-68.0)	5	100.0	0.059
Neuro-ophthalmology	19	20.7 ± 18.0	20.5 (0.0-60.0)	32.4 ± 21.9	36.0 (0.5-64.0)	6	31.6	0.085
OA/OCA	4	0.5 ± 1.0	0.0 (0.0-2.0)	13.2 ± 20.7	4.0 (0.7-44.0)	1	25.0	0.35
High myopia	9	1.3 ± 2.0	0.5 (0.0-5.0)	4.1 ± 3.2	2.7 (1.0-10.0)	4	44.4	0.74
Ocular tumours	17	2.5 ± 3.2	2.0 (0.0-11.0)	14.2 ± 12.5	9.5 (0.6-34.0)	5	29.4	0.070
Others	2	4.3 ± 0.4	4.3 (4.0-4.5)	4.5 ± 0.7	4.5 (4.0-5.0)	1	50.0	1.00
Total	130*					67	51.5	

Abbreviations: MAC = microphthalmia, anophthalmia, and coloboma; OA = ocular albinism; OCA = oculocutaneous albinism; SD = standard deviation

* Fifteen patients presented with overlapping phenotypes and were included in more than one disease category

† Calculated as No. of confirmed diagnosis / No. of patients tested in the same category

‡ Calculated using Fisher's exact test to compare the proportion of confirmed diagnoses in each disease category versus all others

TABLE 3. Genetic testing outcomes and time lapse between onset and first encounter*

	No. of patients tested	Positive genetic test results	Negative genetic test results	P value†	Time lapse between onset and first encounter, y		P value‡
					No. of patients	Mean ± SD	
Family history							
Yes	41	27 (65.9%)	14 (34.1%)	0.037	39	13.1 ± 11.5	0.039
No	89	40 (44.9%)	49 (55.1%)		82	8.5 ± 11.0	
Syndromic condition							
Syndromic	43	31 (72.1%)	12 (27.9%)	0.0014	35	9.6 ± 11.5	0.81
Non-syndromic	87	36 (41.4%)	51 (58.6%)		86	10.1 ± 11.3	

* Data are shown as No. (%), unless otherwise specified

† Calculated using Fisher's exact test for categorical variables

‡ Calculated using independent samples *t* test for continuous variables

consistent with autosomal recessive inheritance.[8] Following detailed phenotypic correlation and variant curation, 16 previously unreported novel variants were confirmed to contribute to molecular diagnoses within this cohort.

A significant difference in the proportion of positive genetic test results was observed between patients with and without a family history of ocular conditions (P=0.037). However, among patients with a family history, the interval between symptom onset and the first visit to the genetics clinic was significantly longer. Positive molecular diagnoses were also more likely to be achieved in syndromic patients (P=0.0014) [Table 3].

As shown in Table 4, individuals with bilateral eye involvement had a greater proportion of positive genetic test results (54.9%), although this difference was not statistically significant (P=0.07). Additionally, no significant difference in diagnostic yield was observed according to age at onset (P=0.29).

Diagnostic and clinical utilities

Genomic testing is increasingly recognised as an important tool for establishing new diagnoses or confirming ones, particularly in the context of rare conditions, which are often complex and costly to diagnose, leading to prolonged diagnostic odysseys. Molecular findings may offer additional clinical utility, including: (1) avoidance of unnecessary investigations or treatments; (2) improved prognostic certainty or redirection of clinical care; (3) enhanced surveillance or timely referral for extraocular

TABLE 4. Diagnostic yield of genetic testing by ocular disease site and age at onset

	No. of patients tested	No. of molecularly confirmed diagnoses	Diagnostic yield†	P value‡
Site of eye involvement				0.07
Bilateral	113	62	54.9%	
Unilateral	17	5	29.4%	
Age at onset*, y				0.29
≤5	64	23	35.9%	
6-10	13	9	69.2%	
11-20	14	5	35.7%	
21-30	15	7	46.7%	
31-40	7	3	42.9%	
>40	8	2	25.0%	

* Data not available for all patients
† Calculated as No. of confirmed diagnosis / No. of patients tested in the same category
‡ Calculated using Fisher's exact test (for site of eye disease) and Chi squared test (for age at onset)

TABLE 5. Diagnostic and clinical utilities of genetic testing (n=67)*

	No. of patients with positive test results
Diagnostic utility	
Confirmed prior diagnosis	53 (79.1%)
Refined/established new diagnosis	14 (20.9%)
Novel variants identified	21 (31.3%)
Clinical utility	
Additional assessment/referral for extraocular manifestations	36 (53.7%)
Prognosis/change in direction of care	48 (71.6%)
Avoided unnecessary investigation/treatment	7 (10.4%)
Cascade testing/family counselling	42 (62.7%)
Reproductive planning	20 (29.9%)
More than one clinical utility	50 (74.6%)
Inheritance pattern	
Autosomal dominant	35 (52.2%)
Autosomal recessive	23 (34.3%)
X-linked dominant/recessive	9 (13.4%)

* Data are shown as No. (%)

manifestations; (4) provision of pre-symptomatic or cascade testing for potentially affected family members; and (5) support for reproductive planning.

In total, 14 patients received revised diagnoses after genomic testing, representing 21% of positive cases (Table 5). These new diagnoses were related to syndromic conditions, such as *CTNNB1*-related neurodevelopmental disorders, or involved extraocular features, such as pantothenate kinase–associated neurodegeneration (online supplementary Table 2).

Through medical record review, we determined that approximately 10% of test-positive patients were able to avoid unnecessary investigations and treatments. In two cases, metabolic workups for congenital cataract were discontinued after diagnostic confirmation. One patient with a pathogenic *ABCA4* variant was advised to withhold vitamin A supplementation. In another case, a syndromic diagnosis of *SOX2*-related microphthalmia eliminated the need for repeated magnetic resonance imaging of the brain and prompted clinicians to monitor for other potential systemic associations, enabling timely intervention. Overall, 74.6% of patients experienced at least one clinical benefit as a result of genomic testing. More than 70% of test-positive patients benefited from improved prognostic certainty or a redirection of care. Approximately 30% of patients—or their carrier or affected parents—were offered options for reproductive planning through either prenatal confirmatory testing or preimplantation genetic testing. Table 5 summarises the clinical and diagnostic utilities observed in this study.

Discussion

Molecular findings and diagnostic yield

In this cohort, we reviewed 130 patients who attended the HKCH genetic counselling clinic over a 23-month period. This review offers a snapshot of the local genomic landscape of IEDs. The overall diagnostic yield of molecular testing was 51.5%, which is comparable to previously reported yields, ranging from 25% to 70% depending on phenotype and testing methodology.[6,9-20]

Among IRDs, a highly heterogeneous group, the diagnostic yield was 58%. This finding is consistent with a recent systematic review which reported a yield of 61.3% (95% confidence interval=57.8%-64.7%) across 51 studies of mixed IRD phenotypes.[21] Several studies have demonstrated that well-curated gene panels are as effective as medical exome sequencing in detecting pathogenic variants in patients with IRDs.[16,19-22]

In our cohort of ocular tumours, 29.4% of patients received germline molecular diagnoses; most of these patients had unilateral retinoblastoma with no family history. Neither routine next-generation sequencing nor Sanger sequencing is typically capable of detecting low-level mosaicism. A previous study reported germline *RB1* mutation detection rates ranging from 10% to 55% in unilateral retinoblastoma, which are substantially lower than

those observed in bilateral cases.[23] In the present study, the oculocutaneous albinism/ocular albinism group had the lowest diagnostic yield at 25%. This low yield may be attributed to the small sample size and the predominance of ocular albinism cases, for which previous research has shown a considerably lower molecular diagnostic yield than oculocutaneous albinism.[24]

Four recurrent variants were identified in this cohort (online supplementary Table 2):

1. NM_000350.3 (*ABCA4*): c.1804C>T, p.(Arg602Trp). This variant is present at a very low frequency in the Genome Aggregation Database[25] (gnomAD v2.1.1: 11 in 250 870 alleles), with a predominance in East Asian populations (gnomAD v2.1.1: 5 in 18 364 alleles). The exact carrier risk in our locality requires further research.
2. NM_000330.4 (*RS1*): c.214G>A, p.(Glu72Lys). A missense variant located in exon 4 of the *RS1* gene. This variant is well documented in Chinese populations, where it accounts for 9.2% of variants in individuals with X-linked retinoschisis.[26]
3. NM_178857.6 (*RP1L1*): c.133C>T, p.(Arg45Trp). This hotspot mutation, located in exon 2 of *RP1L1*, is associated with occult macular dystrophy. Although its allele frequency is not particularly enriched in the Chinese population, it has been mentioned in case reports.[27,28]
4. NM_206933.3 (*USH2A*): c.5572+1G>A. A splice-site variant in intron 27 of the *USH2A* gene, which has been documented in the literature.[29] It has a relatively high allele frequency in East Asians (gnomAD v2.1.1: 3 in 249 996 alleles; East Asian subset: 3 in 18 382 alleles).[30]

Another variant, NM_153638.4 (*PANK2*): c.655G>A, p.(Gly219Ser), is a rare missense variant absent from the general population. It was detected in our local database and reported in 2023.[31] Neurodegeneration with brain iron accumulation 1A (OMIM #234200) is caused by biallelic pathogenic variants in *PANK2*. This rare condition is characterised by early-onset retinal degeneration or pigmented retinopathy, followed by subtle neurological deficits such as tremor and extrapyramidal symptoms. Both ocular and neurological features follow a progressive course. Notably, two unrelated patients in our database carried the same *PANK2* variant. A large, population-based study is warranted to determine whether this variant represents a founder mutation in our locality.

Diagnostic and clinical utilities

Genomic testing has advanced considerably over the past decade. As next-generation sequencing technologies (eg, whole-genome sequencing and multi-omics analysis) become more prevalent, diagnostic yields continue to improve.[32] Given the availability of existing therapies, such as voretigene neparvovec for *RPE65*-related diseases, clinical trials are increasingly investigating gene-based therapies, including gene replacement through viral vectors, mutation suppression via small molecules, and splice modulation using antisense oligonucleotides.[33,34] In addition to ending the diagnostic odyssey, a molecular diagnosis informs clinical management, facilitates access to other clinical services, initiates surveillance for extraocular manifestations, and supports family planning.[6,12,35]

Disease prognostication is a key aspect of clinical utility, most commonly reported in the IRD group. For example, *COL2A1*-related Stickler syndrome carries a high risk of retinal detachment, which may be mitigated through prophylactic cryotherapy or laser retinopexy.[36-38] Among patients with unilateral retinoblastoma, those harbouring germline variants require closer surveillance of the contralateral eye and enhanced vigilance for the potential development of other cancers later in life.[39,40]

Among the 67 test-positive patients, 35 were diagnosed with autosomal dominant conditions (Table 5), six of which were inherited from an affected parent. Approximately one-third of positive findings were attributed to autosomal recessive conditions, with both parents identified as heterozygous carriers. Nine patients had X-linked conditions; in nearly all cases, the mothers were confirmed as heterozygous carriers, except for two who declined genetic testing. In this context, molecular diagnosis is clearly beneficial for cascade screening and reproductive planning. In practice, however, the extent to which patients report these benefits is often influenced by age and family circumstances within the study cohort. As a result, direct comparisons of reported utility across studies remain challenging.

Limitations and strengths

In Hong Kong, our genetic counselling department serves as the major referral centre, receiving patients from both public and private sectors. Individuals with more severe phenotypes are more likely to be referred, resulting in potential ascertainment bias.

Genomic testing was recommended by clinical geneticists based on the clinical phenotype. However, due to resource limitations, not all patients underwent the full spectrum of available tests, which may have resulted in an underestimation of the diagnostic yield. Additionally, certain clinical subgroups (eg, microphthalmia, anophthalmia, and coloboma) had limited sample sizes, potentially affecting diagnostic yield outcomes. Despite these limitations, this pilot study provides a reliable estimate of the mutational spectrum and diagnostic yield among local IED patients.

To our knowledge, this is the first retrospective

study of IED patients to examine both the local genetic landscape and the clinical utility of genomic testing. Our findings highlight the importance of integrating modern genomic technologies into the management of patients with IEDs. They also underscore the need for an enhanced service model through a multidisciplinary team approach, implemented via a combined ocular genetics clinic.

Ideally, clinical utility should be assessed through a randomised controlled trial, which maximises internal validity and control for confounding variables. However, the level of evidence required varies according to clinical indication and type of genetic test. The data presented in this retrospective observational study, collected over nearly 2 years, are considered representative of real-world clinical scenarios. Future research involving multicentre collaborations over a longer period (eg, 10 years) will provide a more comprehensive understanding.

Ocular genetics clinic: a new service model in Hong Kong

Interestingly, patients with a family history experienced a longer interval between symptom onset and their first encounter at the clinical genetics clinic (Table 3). This finding emphasises the importance of raising public awareness about the role of genomic medicine in managing IEDs.

The multidisciplinary team clinic model—comprising ophthalmologists, genetic counsellors, geneticists, and genetic nurses—is a current global trend for integrating genomic testing into clinical care pathways. It has been proven effective, particularly when applied to IRDs as a model.[41,42] Similar models have also been adopted in other specialties, such as neurogenetics and cardiogenetics clinics.

At HKCH, a combined ocular genetics clinic commenced service in May 2022. The team includes ophthalmologists, genetic counsellors, clinical geneticists, optometrists, and nurses. Patients are referred from both public and private sectors for a variety of indications, such as atypical eye phenotypes, suspected syndromic conditions, or complex counselling needs (eg, variants of uncertain clinical significance detected in previous genomic tests conducted locally or overseas). This one-stop combined clinic enables joint discussions among specialists to formulate comprehensive management plans and reduces the need for repeated hospital visits, saving patients valuable time.

Conclusion

Approximately 4% of patients attending our genetic clinic had ocular disorders. The overall diagnostic yield of genomic testing was 51.5%; predominance was the strongest among patients with syndromic presentations and positive family history.

This study demonstrates high clinical utility of genomic testing in over 70% of patients with confirmed molecular diagnoses. There is a global shift towards managing IED patients through a multidisciplinary team clinic service model. To meet the growing demand for genomic medicine in IEDs, future studies should incorporate prospective, population-wide sampling, long-term follow-up, and multicentre collaboration.

Author contributions

Concept or design: SSW Cheng, HM Luk.
Acquisition of data: SSW Cheng.
Analysis or interpretation of data: SSW Cheng, SSL Cheung.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

As an editor of the journal, JCS Yam was not involved in the peer review process. Other authors have disclosed no conflicts of interest.

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Declaration

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Ethics approval

This research was performed in compliance with the Declaration of Helsinki. Ethics approval was granted by the Hospital Authority Central Institutional Review Board, Hong Kong (Ref No.: PAED-2023-076). A waiver of patient consent was obtained from the Committee due to the retrospective nature of the research.

Supplementary material

The supplementary material was provided by the authors and some information may not have been peer reviewed. Accepted supplementary material will be published as submitted by the authors, without any editing or formatting. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by the Hong Kong Academy of Medicine and the Hong Kong Medical Association. The Hong Kong Academy of Medicine and the Hong Kong Medical Association disclaim all liability and responsibility arising from any reliance placed on the content. To view the file, please visit the journal online (https://doi.org/10.12809/hkmj2412298).

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