BMJ Open

Prevalence and associated risk factors in patients with hereditary retinal dystrophy---a nationwide population-based study in Taiwan

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-054111
Article Type:	Original research
Date Submitted by the Author:	04-Jun-2021
Complete List of Authors:	Woon, Peng Yeong; Tzu Chi University, Department of Molecular Biology and Human Genetics Chien, Jia-Ying; Tzu Chi University Wang, Jen-Hung ; Hualien Tzu Chi Medical Center, Department of Medical Research Chou, Yu-Yau; Tzu Chi University, Department of Molecular Biology and Human Genetics Lin, Mei-Chen; China Medical University; China Medical University Hospital Huang, Shun-Ping; Tzu Chi University, Department of Molecular Biology and Human Genetics; Taichung Tzu Chi Hospital, Department of Ophthalmology
Keywords:	OPHTHALMOLOGY, EPIDEMIOLOGY, HEALTH SERVICES ADMINISTRATION & MANAGEMENT

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Prevalence and associated risk factors in patients with hereditary retinal dystrophy---a nationwide population-based study in Taiwan

Peng Yeong Woon[1], Jia-Ying Chien[2], Jen-Hung Wang[3], Yu-Yau Chou[1], Mei-Chen Lin[4, 5], Shun-Ping Huang[1, 2, 6]

[1] Department of Molecular Biology and Human Genetics, Tzu Chi University, Hualien, Taiwan
[2] Institute of Medical Sciences, Tzu Chi University, Hualien, Taiwan
[3]. Department of Medical Research, Tzu Chi General Hospital, Hualien, Taiwan
[4].College of Medicine, China Medical University, Taichung, Taiwan
[5]. Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan
[6].Department of Ophthalmology, Taichung Tzu Chi Hospital, Taichung, Taiwan

Corresponding Author

Shun-Ping Huang
Department of Molecular Biology and Human Genetics,
Tzu Chi University
701, Sec. 3, Chung-Yang Rd, Hualien, 97002, Taiwan
Tel: +886-3-8565301#2694
Fax: +886-3-8561422
E-mail: sphophdoc1688@gms.tcu.edu.tw; sphophdoc1688@gmail.com

Abstract

Objective To study the prevalence, incidence and risk factors associated with hereditary retinal dystrophy in Taiwan from 2000 to 2013

Design, Setting and Participants This is a nationwide, population-based, retrospective case-control study using National Health Insurance Database. Study groups are patients with hereditary retinal dystrophies (HRD) as case group; age-matched patients without any diagnosis of HRD as control group. We enrolled 2,418 study subjects, of which 403 were HRD patients. Important confounding factors such as hypertension, diabetes, coronary artery disease, autoimmune disease, cancer, liver cirrhosis, chronic kidney disease, stroke, hyperlipidemia, asthma, depression and dementia are also included.

Exposure Diagnosis of hereditary retinal dystrophy

Main outcomes and Measures Odds ratio calculated between risk factors and HRD for objects and stratified by age and sex group between 2000 and 2013.

Results Four hundred and three patients were included in the study group and 2015 in the control group. The incidence of HRD was 3.29/100, 000, and prevalence of HRD was 40.5/100,000 persons. The study group was more like to have cataract, cystoid macula edema (CME) than the control group. Among the subgroup with comorbidities, the risk of hypertension, diabetes and chronic kidney disease was significantly higher among HRD patients who younger than 55 years old.

Conclusions 74% of the diagnosed HRD are retinitis pigmentosa. Population-based data suggested an increased risk of cataract in younger patients, whereas older HRD patients are more susceptible to develop CME. Future work is needed to elucidate the mechanism between these ophthalmologic disorders and HRD.

Strengths and limitation of this study

- We conducted a nationwide, population-based study to explore the prevalence, incidence and risk factors associated with hereditary retinal dystrophy in Taiwan
- Our study suggested an increased risk of cataract in younger hereditary retinal dystrophy patients whereas older patients are more susceptible to develop cystoid macular edema.
- Younger patients with hereditary retinal dystrophy have a higher risk to develop hypertension, diabetes and chronic kidney diseases.
- Regular screening and monitor HRD patients with optical coherence tomography, blood pressure, levels of electrolytes and blood sugar were highly recommended.

Introduction

Hereditary retinal dystrophies (HRD), such as retinitis pigmentosa (RP), Cone dystrophy, Stargardt disease, Usher syndrome, Leber's congenital amaurosis, retinoschisis, etc., are a group of genetic retinal disorders exhibiting both genetic and phenotypic heterogeneity with a collectively estimated incidence of 1:2000 to 1:3000[1-3]. Among HRD, retinitis pigmentosa, one of the most common forms with variable clinical manifestations, affects approximately 1 in 3000 to 4000 people worldwide[4, 5].

To date, there is more than 271 genes (Retnet: https://sph.uth.edu/retnet/, last update January 21, 2021) associated with HRD have been identified. The clinical manifestations of HRD patients may vary according to complexity of the genetic background and most common features include night blindness, constricted visual field, color vision deficiency or even total blindness. The other ocular complications such as cataract, cystoid macular edema (CME), or epiretinal membrane, will further deteriorate central vision and increase activity limitation at younger age. A wide range prevalence of these complications in HRD has been reported in different studies. Accurate assessment will help identified these complications and foster the development of advanced therapeutic approaches.

The aim of this study is to explore the prevalence and risk factors associated with HRD in a nationwide, population-based, retrospective case-control study using Taiwan National Health Insurance (NHI) Database. The NHI database was used to retrieve cases of HRD to observe the events of cataract, CME, epiretinal membrane, retinoschisis and other covariates.

Materials and Methods

Data source

This was a nationwide population-based retrospective case-control study. The National Health Insurance (NHI) program, which was implemented in Taiwan on March 1, 1995, built a high coverage health database, named National Health Insurance Database (NHIRD) and enrolled over 99% of population in Taiwan as of today. The records of outpatients, hospitalization, medical treatment, and other medical services of each hospital visit were included in the database. We conducted the analysis by using Longitudinal Health Insurance Database 2000 (LHID 2000), the subset of NHIRD. LHID 2000 consisted of 1 million study subjects, which was randomly sampled from NHIRD and made sure they were already insured in the year 2000. The database was for medical research and the identification numbers of all individuals were encrypted to protect the privacy of the individuals. The diagnoses in Taiwan NHIRD are defined according to the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM). The study was approved by the Research Ethics Committee of China Medical University and Hospital in Taiwan (CMUH-104-REC2-115-R4).

Study subjects

We identified 403 subjects from the LHID2000 with the diagnosis of hereditary retinal dystrophies (HRD) (ICD-9-CM Code 362.7x) made between 1 January 2000 and 31 December 2013. The index date for a HRD subject was the date when the disease was first coded.

Control Group

Control patients were defined as subjects without any diagnosis of HRD and were pair matched to the subjects with HRD by age, sex, and index date in a ratio of 5 controls to each HRD subject.

Patient and public involvement

There was no patient or public involvement in this study.

Risk factors and other covariates

The risk factors we discussed included cataract (ICD-9: 366.X or Pseudophakia

(V43.1) or procedure code: 86007C, 86008C, 86009C, 86010B), cystoid macular edema (ICD-9: 362.53), retinoschisis (ICD-9:361.1), epiretinal membrane (ICD-9: 362.56), retinal detachment (ICD-9: 361.0), and YAG capsulotomy (procedure code: 60013C, 60014C), which had diagnosis record within 1 year before the index date. Some comorbidities were included as other covariates. These comorbidities were important confounding factors in this study. We defined the comorbidities occurred one year before the index date and with at least twice outpatients or once hospitalization record. Hypertension (ICD-9: 401-405, A260, A269), diabetes (ICD-9: 250, A181), coronary artery disease (ICD-9: 410-414, A270, A279), autoimmune disease (ICD-9: 710, 714), cancer (ICD-9: 140-208), liver cirrhosis (ICD-9: 571.2, 571.5, 571.6), chronic kidney disease (ICD-9: 582, 583, 585, 586, 588), stroke (ICD-9: 430-438), hyperlipidemia (ICD-9: 272, A182), asthma (ICD-9: 493), depression (ICD-9: 296.2, 296.3, 296.82, 300.4, 309.0, 309.1, 309.28, 311) and dementia (ICD-9: 290, 294.1, 331.0) were included.

Statistical analysis

The annual incidence rate of HRD was calculated by the annual newly diagnosed HRD patients divided by every 100,000 person-year. The difference of demographic and comorbidities between two groups was compared by chi-square/ Fisher exact test and t-test for categorical and continuous variable, respectively and the risk factors of HRD was evaluated by conditional logistic regression and shown by odds ratio (OR), adjusted odds ratio (aOR) and 95% confidence interval (95% C.I.). All statistical analyses were carried out using Statistical Analysis Software (SAS), version 9.4 (SAS Institute Inc., Cary, NC, United States). The significant criteria set at two side p-value less than 0.05.

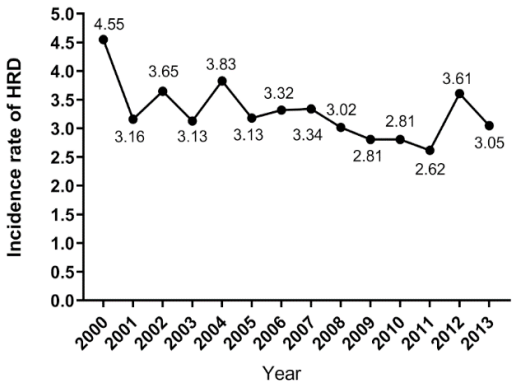
Results

HRD incidence

Table 1 presented the annual incidence rate of HRD from 2000 to 2013. The incidence rate of HRD showed approximately 2.62-4.55 every 100,000 person-year, with an average rate of approximately 3.29 every 100, 000 person-year in Taiwan. The annual incidence showed similar during the 14 years follow up.

Table 1. Incidence of HRD from 2000 to 2013

Year	HRD	Total Population Person Years	Annual Incidence Rate per 100,000 person years
2000	42	922354	4.55
2001	29	918184	3.16
2002	33	903289	3.65
2003	28	893619	3.13
2004	34	887334	3.83
2005	28	881009	3.18
2006	29	874763	3.32
2007	29	868228	3.34
2008	26	861413	3.02
2009	24	854379	2.81
2010	24	854379	2.81
2011	22	839714	2.62
2012	30	831452	3.61
2013	25	819168	3.05



Demographics

Table 2 presented the demographic, risk factors and comorbidities of study subjects. We totally enrolled 2,418 study subjects, including 403 HRD patients and 2,015 non-HRD patients, and the mean age was 49 years old. After comparing the prevalence of risk factors and between HRD and non-HRD group, HRD patients showed significant higher prevalence of cataract ($p<0.001$), CME ($p<0.001$), posterior capsulotomy ($p=0.035$), hypertension ($p=0.016$), diabetes ($p<0.001$), chronic kidney disease ($p=0.013$) and hyperlipidemia than non-HRD patients. Retinitis pigmentosa accounted for 74% of HRD diagnosis.

Table 2. Characteristics of patients with or without HRD

Table 2. Characteristics of patients with or without HRD

	Total N=2418	Non-HRD (n=2015)	HRD (n=403)	p-value
	n	n (%) / mean(SD)	n (%) / mean(SD)	
Gender				1.000
Female	1242	1035 (51.4)	207 (51.4)	
Male	1176	980 (48.6)	196 (48.6)	
Age, years				1.000
<20	210	175 (8.68)	35 (8.68)	
20-39	552	460 (22.83)	92 (22.83)	
40-59	876	730 (36.23)	146 (36.23)	
≥60	780	650 (32.26)	130 (32.26)	
mean(SD)[a]		49.1 (18.7)	49.2 (18.6)	0.939
Risk factors				
Cataract	64	31 (1.5)	33 (8.2)	<0.001
Cystoid macular edema	35	9 (0.5)	26 (6.5)	<0.001
Retinal detachment[b]	4	2 (0.1)	2 (0.5)	0.132
Retinoschisis[b]	1	0 (0.0)	1 (0.3)	0.167
Posterior Capsulotomy	13	8 (0.4)	5 (1.2)	0.035
Epiretinal membrance[b]	3	1 (0.1)	2 (0.5)	0.074
Comorbidity				
Hypertension	471	375 (18.6)	96 (23.8)	0.016
Diabetes	241	176 (8.7)	65 (16.1)	<0.001
Coronary artery disease	127	101 (5)	26 (6.5)	0.237
Autoimmune diseases[b]	1	0 (0)	1 (0.2)	0.167
Malignancies	13	12 (0.6)	1 (0.2)	0.384
Liver cirrhosis	10	9 (0.4)	1 (0.2)	0.571
Chronic kidney disease	34	23 (1.1)	11 (2.7)	0.013
Cerebrovascular disease	98	87 (4.3)	11 (2.7)	0.140
Hyperlipidemia	228	176 (8.7)	52 (12.9)	0.009
Asthma	56	45 (2.2)	11 (2.7)	0.545
Depression	49	38 (1.89)	11 (2.73)	0.273
Dementia	25	22 (1.09)	3 (0.74)	0.529
Retinitis Pigmentosa, RP		-	300 (74.4)	

[a]t-test

[b]Fisher exact test

Factors associated with HRD

Table 3 revealed the crude and adjusted odds ratio of having HRD for subjects with or without some ocular diseases or comorbidity with the adjustment for age, sex and comorbid diseases. Patients with HRD were significantly associated with cataract (aOR=6.03, 95% CI=3.60-10.10) and CME (aOR=14.64, 95% CI=6.78-31.60), but not with epiretinal membrane, retinal detachment, depression or dementia. The development of CME in HRD patients is correlated to age. The prevalence rate of CME in HRD patients older than 55 years (9.4%) is higher than the HRD patients younger than 55 years (4.5%).

Table 3. Odds Ratios and 95% Confidence Intervals of HRD associated with eye diseases and comorbidities

Table 3. Odds Ratios and 95% Confidence Intervals of HRD Associated With eye diseases and comorbidities

Characteristics	OR (95% CI)	p value	aOR (95% CI)	p value
Cataract				
No	Ref.		Ref.	
Yes	5.68 (3.44-9.40)	<0.001	6.03 (3.60-10.10)	<0.001
Cystoid macular edema				
No	Ref.		Ref.	
Yes	14.68 (6.86-31.41)	<0.001	14.64 (6.78-31.60)	<0.001
Retinal detachment				
No	Ref.		Ref.	
Yes	5.00 (0.70-35.50)	0.108	5.15 (0.71-37.38)	0.105
Retinoschisis				
No	Ref.		Ref.	
Yes	-	-	-	-
Posterior Capsulotomy				
No	Ref.		Ref.	
Yes	3.17 (1.03-9.79)	0.045	2.96 (0.90-9.74)	0.074
Epiretinal membrance				
No	Ref.		Ref.	
Yes	8.39 (0.74-94.51)	0.085	-	-
Depression				
No	Ref.		Ref.	
Yes	1.46 (0.74-2.88)	0.276	1.31 (0.65-2.63)	0.449
Dementia				
No	Ref.		Ref.	
Yes	0.65 (0.18-2.31)	0.509	0.76(0.20-2.91)	0.689

Abbreviation: OR, odds ratio; CI, confidence interval

Stratification analysis

Table 4-1 and 4-2 showed the characteristics of patients with or without HRD stratified by age. Among subjects who were older than 55 years, HRD group had significant higher prevalence of cataract (p=0.002), CME (p<0.001), diabetes (p<0.001) and hyperlipidemia (p=0.028). Similarly, HRD group had significant higher prevalence of cataract (p<0.001), CME (p<0.001), posterior capsulotomy (p=0.005), hypertension (p=0.001), diabetes (p=0.035) and chronic kidney disease (p=0.017) among subjects who younger than 55 years old.

Table 4-1. Characteristics of patients older than 55 y/o with or without HRD

	Total	Non-HRD	HRD	p-value
	n	n (%)	n (%)	
Age, ≧55 years				
Risk factors				
Cataract	40	26 (3.2)	14 (8.7)	0.002
Cystoid macular edema	24	9 (1.1)	15 (9.3)	<0.001
Retinal detachment	0	0 (0.0)	0 (0.0)	-
Retinoschisis	3	2 (0.2)	1 (0.6)	0.422
Posterior Capsulotomy	10	8 (1)	2 (1.2)	0.676
Epiretinal membrance	2	0 (0.0)	2 (0.8)	0.028
Comorbidity				
Hypertension	373	305 (37.9)	68 (42.2)	0.301
Diabetes	190	139 (17.3)	51 (31.7)	<0.001
Chronic kidney disease	27	20 (2.5)	7 (4.3)	0.190
Hyperlipidemia	170	132 (16.4)	38 (23.6)	0.028

Table 4-2. Characteristics of patients younger than 55 y/o with or without HRD

	Total	Non-HRD	HRD	p-value
	n	n (%)	n (%)	
Age, <55 years				
Risk factors				
Cataract	24	5 (0.4)	19 (7.9)	<0.001
Cystoid macular edema	11	0 (0.0)	11 (4.5)	<0.001
Retinal detachment	1	0 (0.0)	1 (0.4)	0.167
Retinoschisis	1	0 (0.0)	1 (0.4)	0.167
Posterior Capsulotomy	3	0 (0.0)	3 (1.2)	0.005
Epiretinal membrance	1	1 (0.1)	0 (0.0)	1.000
Comorbidity				
Hypertension	98	70 (5.8)	28 (11.6)	0.001
Diabetes	51	37 (3.1)	14 (5.8)	0.035
Chronic kidney disease	7	3 (0.2)	4 (1.7)	0.017
Hyperlipidemia	58	44 (3.6)	14 (5.8)	0.119

After stratification by age and gender (Table 5), patients who were male (aOR=7.00, 95% CI=3.37-14.54), female (aOR=5.22, 95% CI=2.47-11.05), younger (aOR=22.01, 95% CI=7.86-61.65) or older than 55 years (aOR=3.08, 95% CI=1.55-6.11) with cataract showed significant association with HRD, aOR was higher especially among patients younger than 55 years old (Table 5). CME also showed significant association with HRD among male (aOR=14.89, 95% CI=5.21-42.60), female (aOR=14.77, 95% CI=4.73-46.06) and patients who are older than 55 years (aOR=8.07, 95% CI=3.43-19.03).

Table 5. Odds ratio and confidence intervals of HRD in different stratification.

Variables	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Cataract				
Gender				
Female	4.32 (2.10-8.90)	<0.001	5.22 (2.47-11.05)	<0.001
Male	7.40 (3.63-15.09)	<0.001	7.00 (3.37-14.54)	<0.001
Age at baseline				
<55	20.68 (7.60-56.23)	<0.001	22.01 (7.86-61.65)	<0.001
≥55	2.80 (1.44-5.46)	0.002	3.08 (1.55-6.11)	0.001
Cystoid macular edema				
Gender				
Female	16.83 (5.45-52.03)	<0.001	14.77 (4.73-46.06)	<0.001
Male	13.00 (4.64-36.47)	<0.001	14.89 (5.21-42.60)	<0.001
Age at baseline				
<55	-		-	
≥55	8.48 (3.70-19.47)	<0.001	8.07 (3.43-19.03)	<0.001

Discussions:

In this retrospective case control study using NHI database, the prevalence of cataract, CME, epiretinal membrane, retinal detachment and retinoschisis in HRD patients (n=403) was 8.2%, 6.5%, 0.5%, 0.5% and 0.3%. Compared with individuals without HRD, patients with HRD had a higher incidence of cataract (8.2% vs 1.5%, p<0.001) and CME (6.5% vs 0.5 %, p<0.001) and HRD patients aged younger than 55 years had an increased risk of hypertension, diabetes and chronic kidney disease. These data indicate the prevalence of potentially treatable HRD related ocular complications is relatively high and the comorbidities are more likely to be developed at younger HRD patients.

The reported prevalence of CME in patient with HRD especially RP ranges from 14% to 23 % as evaluated by fluorescein angiography (FA)[6-8], 7.5% to 49% as evaluated by time domain OCT (TD-OCT)[9-12] and 12.5% to 58.6%[13-18] as evaluated by spectral domain OCT (SD-OCT). However, these reports mostly were single-hospital study and were non-population-based data which cannot be able to calculate exact prevalence rate of CME. Our prevalence for CME (6.5%) is relatively lower than the previous reports but similar to the studies by Oishi et al[11]., detected CME in 49 eyes (7.5%) out of 652 eyes of 326 patients and Hagiwara et al[19]., reported CME was detected in 26 (8%) out of 323 patients with RP using TD-OCT. The big discrepancy in CME prevalence rate among the studies may associated with different definition of CME, different detection methods and equipment or different populations. The exact etiology of CME in HRD remains uncertain and various proposed pathophysiological mechanisms, such as breakdown of the blood-retinal barrier[20, 21], Muller cell dysfunction[22], vitreomacular traction[23, 24], anti-retinal autoantibodies[25], and retinal pigment epithelium dysfunction[26], have been suggested[27, 28]. Additionally, further investigation to evaluate the association between CME and the genetic background effects will also be needed.

Patients with HRD usually start developing cataract at younger age compared with normal population. Posterior subcapsular cataract is the most common form of cataract observed in patients with HRD whereas nuclear or cortical cataract is more common in age-related cataract. The severity of cataract in HRD patients is related to the onset age and the duration of disease progression. In Taiwan the prevalence rate of cataract surgery was 0.54% and the incidence rate of first cataract surgery was 0.44% in 2010[29]. Data from

previous reports indicated that higher incidence rate of cataract surgery was observed among women than among men[29-33]. In this study, the prevalence rate of cataract surgery is significantly higher in HRD patients compared with age-matched non-HRD people (8.3% vs 1.3%; p<0.001). Adjusted OR of cataract in HRD patients younger than 55 y/o and older than 55 y/o is 22.01 (95% CI=7.86-61.65) and 3.05 (95% CI=1.55-6.11) respectively. Our results suggest that cataract occurred at younger age and more frequently among man than among women in HRD patients (Table 5).

In this study, HRD subjects younger than 55y/o had a higher prevalence of hypertension, diabetes, and chronic kidney diseases than the age-matched control subjects while HRD subjects older than 55y/o had a higher prevalence of diabetes and hyperlipidemia than the age-matched control subject. The association between these comorbidities and HRD is unclear. Some individuals with HRD may have other associated non-ocular diseases[2, 34]. Patients with Bardet-Biedl syndrome (BBS) [35, 36], Alstrom syndrome (AS)[37, 38], Kearns-Sayre syndrome [39, 40] and Wolfram syndrome[41, 42], have been reported to have the combination of diabetes and retinal dystrophy. BBS and AS patients usually show the symptoms of obesity and impaired renal function while Senior-Loken syndrome patients are not obese but present with severe renal dysfunction[43, 44]. The pathophysiological mechanisms underlying the high prevalence of these comorbidities in HRD patients should be further investigated.

The central vision of HRD patients may be compromised not only by primary disease process but also by the complications occurring as the diseases progresses. CME and cataract are the main risk factors of central visual deteriorating in patients with HRD. Those complications may be solved with surgery or medication, resulting in improved anatomical and visual outcomes

Limitations

This case-control retrospective study has limitations. First, the NHI database does not provide information regarding personal physical activity, nutrition, lifestyles, body mass index or metabolic profiles affecting the risks of hypertension, hyperlipidemia, diabetes and chronic kidney diseases. Second, the ICD-9-CM codes for the diagnosis of HRD and the comorbid diseases were less precise than the data collected through standardized examination. Furthermore, there is no specific code for each different HRD, such as cone-rod dystrophy, Stargardt diseases, Usher syndrome, Leber's congenital

amaurosis and other retinal dystrophy associated syndromes. Third, we may have underestimated the prevalence of CME in HRD subjects since there was no standard criteria to define cystoid macular edema on OCT sans from the NHI database.

Conclusions

These finding from our nationwide, population-based case control study suggests an increased risk of cataract in younger HRD patients, whereas older HRD patients are more susceptible to develop CME. Understanding the pathophysiological mechanisms between these ocular complications and HRD will help to develop effective therapies to improve patients' vision. Furthermore, younger HRD patients have a higher risk to develop hypertension, diabetes and chronic kidney diseases. Regular screening and monitor HRD patients with optical coherence tomography (OCT), blood pressure, levels of electrolytes and blood sugar will help maintain useful central vision and prevent vascular, metabolic and renal comorbidities.

Footnotes

Contributors: Conceptualization, SP.H. and JH.W.; methodology, software, validation, and formal analysis, MC.L.; resources, SP.H.; writing—original draft preparation, PY.W., JY.C., JH.W., YY.C. and MC.L..; writing—review and editing, JH.W. and SP.H.; supervision, SP.H; funding acquisition, SP.H. All authors have read and agreed to the published version of the manuscript.

Funding: This study was supported in part by Collaborative Grant by Tzu Chi Medical Foundation and Tzu Chi University To: Shun-Ping Huang TCAS-107-02, Taiwan Ministry of Health and Welfare Clinical Trial Center (MOHW109-TDU-B-212-114004), MOST Clinical Trial Consortium for Stroke (MOST 109-2321-B-039-002), Tseng-Lien Lin Foundation, Taichung, Taiwan.

Competing interests: The authors declare no financial support or conflict of interest.

Patient consent: Not required

Ethics approval

This study was approved by the Research Ethics Committee of China Medical University and Hospital in Taiwan approved the study (CMUH-104-REC2-115-(AR4)).

Data sharing statement: No additional data available

References

1. Broadgate S, Yu J, Downes SM, Halford S. Unravelling the genetics of inherited retinal dystrophies: Past, present and future. Progress in retinal and eye research 2017;59:53-96.
2. Hartong DT, Berson EL, Dryja TP. Retinitis pigmentosa. Lancet (London, England) 2006;368:1795-809.
3. Hamel CP. Gene discovery and prevalence in inherited retinal dystrophies. Comptes rendus biologies 2014;337:160-6.
4. Boughman JA, Conneally PM, Nance WE. Population genetic studies of retinitis pigmentosa. American journal of human genetics 1980;32:223-35.
5. Heckenlively JR, Yoser SL, Friedman LH, Oversier JJ. Clinical findings and common symptoms in retinitis pigmentosa. American journal of ophthalmology 1988;105:504-11.
6. Newsome DA. Retinal fluorescein leakage in retinitis pigmentosa. Am J Ophthalmol 1986;101:354-60.
7. Fishman GA, Fishman M, Maggiano J. Macular lesions associated with retinitis pigmentosa. Archives of ophthalmology (Chicago, Ill : 1960) 1977;95:798-803.
8. Fishman GA, Maggiano JM, Fishman M. Foveal lesions seen in retinitis pigmentosa. Archives of ophthalmology (Chicago, Ill : 1960) 1977;95:1993-6.
9. Hirakawa H, Iijima H, Gohdo T, Tsukahara S. Optical coherence tomography of cystoid macular edema associated with retinitis pigmentosa. American journal of ophthalmology 1999;128:185-91.
10. Chung H, Hwang JU, Kim JG, Yoon YH. Optical coherence tomography in the diagnosis and monitoring of cystoid macular edema in patients with retinitis pigmentosa. Retina (Philadelphia, Pa) 2006;26:922-7.
11. Oishi A, Otani A, Sasahara M, et al. Photoreceptor integrity and visual acuity in cystoid macular oedema associated with retinitis pigmentosa. Eye (London, England) 2009;23:1411-6.
12. Adackapara CA, Sunness JS, Dibernardo CW, Melia BM, Dagnelie G. Prevalence of cystoid macular edema and stability in oct retinal thickness in eyes with retinitis pigmentosa during a 48-week lutein trial. Retina (Philadelphia, Pa) 2008;28:103-10.
13. Triolo G, Pierro L, Parodi MB, et al. Spectral domain optical coherence tomography findings in patients with retinitis pigmentosa. Ophthalmic research 2013;50:160-4.
14. Iovino C, Au A, Hilely A, et al. Evaluation of the Choroid in Eyes With Retinitis Pigmentosa and Cystoid Macular Edema. Investigative ophthalmology

& visual science 2019;60:5000-5006.
15. Kim YJ, Joe SG, Lee DH, Lee JY, Kim JG, Yoon YH. Correlations between spectral-domain OCT measurements and visual acuity in cystoid macular edema associated with retinitis pigmentosa. Investigative ophthalmology & visual science 2013;54:1303-9.
16. Hajali M, Fishman GA, Anderson RJ. The prevalence of cystoid macular oedema in retinitis pigmentosa patients determined by optical coherence tomography. The British journal of ophthalmology 2008;92:1065-8.
17. Hajali M, Fishman GA. The prevalence of cystoid macular oedema on optical coherence tomography in retinitis pigmentosa patients without cystic changes on fundus examination. Eye (London, England) 2009;23:915-9.
18. Liew G, Strong S, Bradley P, et al. Prevalence of cystoid macular oedema, epiretinal membrane and cataract in retinitis pigmentosa. Br J Ophthalmol 2019;103:1163-1166.
19. Hagiwara A, Yamamoto S, Ogata K, et al. Macular abnormalities in patients with retinitis pigmentosa: prevalence on OCT examination and outcomes of vitreoretinal surgery. Acta ophthalmologica 2011;89:e122-5.
20. Vinores SA, Kuchle M, Derevjanik NL, et al. Blood-retinal barrier breakdown in retinitis pigmentosa: light and electron microscopic immunolocalization. Histology and histopathology 1995;10:913-23.
21. Spalton DJ, Rahi AH, Bird AC. Immunological studies in retinitis pigmentosa associated with retinal vascular leakage. The British journal of ophthalmology 1978;62:183-7.
22. Makiyama Y, Oishi A, Otani A, et al. Prevalence and spatial distribution of cystoid spaces in retinitis pigmentosa: investigation with spectral domain optical coherence tomography. Retina (Philadelphia, Pa) 2014;34:981-8.
23. Schepens CL, Avila MP, Jalkh AE, Trempe CL. Role of the vitreous in cystoid macular edema. Survey of ophthalmology 1984;28 Suppl:499-504.
24. Takezawa M, Tetsuka S, Kakehashi A. Tangential vitreous traction: a possible mechanism of development of cystoid macular edema in retinitis pigmentosa. Clinical ophthalmology (Auckland, NZ) 2011;5:245-8.
25. Heckenlively JR, Aptsiauri N, Nusinowitz S, Peng C, Hargrave PA. Investigations of antiretinal antibodies in pigmentary retinopathy and other retinal degenerations. Transactions of the American Ophthalmological Society 1996;94:179-200; discussion 200-6.
26. Heckenlively JR, Solish AM, Chant SM, Meyers-Elliott RH. Autoimmunity in hereditary retinal degenerations. II. Clinical studies: antiretinal antibodies and fluorescein angiogram findings. The British journal of ophthalmology

1985;69:758-64.
27. Strong S, Liew G, Michaelides M. Retinitis pigmentosa-associated cystoid macular oedema: pathogenesis and avenues of intervention. The British journal of ophthalmology 2017;101:31-37.
28. Strong SA, Hirji N, Quartilho A, Kalitzeos A, Michaelides M. Retrospective cohort study exploring whether an association exists between spatial distribution of cystoid spaces in cystoid macular oedema secondary to retinitis pigmentosa and response to treatment with carbonic anhydrase inhibitors. The British journal of ophthalmology 2019;103:233-237.
29. Lee JS, Chung CC, Lin KK, Yu KH, Kuo CF, See LC. Time trends in cataract surgery and after-cataract laser capsulotomy in Taiwan: A population-based retrospective cohort study. Int J Surg 2016;36:265-273.
30. Gollogly HE, Hodge DO, St Sauver JL, Erie JC. Increasing incidence of cataract surgery: population-based study. J Cataract Refract Surg 2013;39:1383-9.
31. Semmens JB, Li J, Morlet N, Ng J. Trends in cataract surgery and postoperative endophthalmitis in Western Australia (1980-1998): the Endophthalmitis Population Study of Western Australia. Clin Exp Ophthalmol 2003;31:213-9.
32. Behndig A, Montan P, Stenevi U, Kugelberg M, Lundström M. One million cataract surgeries: Swedish National Cataract Register 1992-2009. J Cataract Refract Surg 2011;37:1539-45.
33. Lundström M, Goh PP, Henry Y, et al. The changing pattern of cataract surgery indications: a 5-year study of 2 cataract surgery databases. Ophthalmology 2015;122:31-8.
34. Verbakel SK, van Huet RAC, Boon CJF, et al. Non-syndromic retinitis pigmentosa. Progress in retinal and eye research 2018;66:157-186.
35. O'Dea D, Parfrey PS, Harnett JD, Hefferton D, Cramer BC, Green J. The importance of renal impairment in the natural history of Bardet-Biedl syndrome. American journal of kidney diseases : the official journal of the National Kidney Foundation 1996;27:776-83.
36. Mujahid S, Hunt KF, Cheah YS, et al. The Endocrine and Metabolic Characteristics of a Large Bardet-Biedl Syndrome Clinic Population. The Journal of clinical endocrinology and metabolism 2018;103:1834-1841.
37. Tsang SH, Aycinena ARP, Sharma T. Ciliopathy: Alstrom Syndrome. Advances in experimental medicine and biology 2018;1085:179-180.
38. Millay RH, Weleber RG, Heckenlively JR. Ophthalmologic and systemic manifestations of Alstrom's disease. American journal of ophthalmology

1986;102:482-90.
39. Boltshauser E, Gauthier G. Diabetes Mellitus in Kearns-Sayre syndrome. American journal of diseases of children (1960) 1978;132:321-2.
40. Finsterer J, Frank M. Diabetes in Kearns-Sayre Syndrome: More Common than Anticipated. Canadian journal of diabetes 2015;39:253.
41. d'Annunzio G, Minuto N, D'Amato E, et al. Wolfram syndrome (diabetes insipidus, diabetes, optic atrophy, and deafness): clinical and genetic study. Diabetes care 2008;31:1743-5.
42. Reschke F, Rohayem J, Maffei P, et al. Collaboration for rare diabetes: understanding new treatment options for Wolfram syndrome. Endocrine 2021;71:626-633.
43. Hildebrandt F, Waldherr R, Kutt R, Brandis M. The nephronophthisis complex: clinical and genetic aspects. The Clinical investigator 1992;70:802-8.
44. Hildebrandt F, Zhou W. Nephronophthisis-associated ciliopathies. Journal of the American Society of Nephrology : JASN 2007;18:1855-71.

BMJ Open

Prevalence and associated relating factors in patients with hereditary retinal dystrophy---a nationwide population-based study in Taiwan

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-054111.R1
Article Type:	Original research
Date Submitted by the Author:	11-Dec-2021
Complete List of Authors:	Woon, Peng Yeong; Tzu Chi University, Department of Molecular Biology and Human Genetics Chien, Jia-Ying; Tzu Chi University Wang, Jen-Hung ; Hualien Tzu Chi Medical Center, Department of Medical Research Chou, Yu-Yau; Tzu Chi University, Department of Molecular Biology and Human Genetics Lin, Mei-Chen; China Medical University; China Medical University Hospital Huang, Shun-Ping; Tzu Chi University, Department of Molecular Biology and Human Genetics; Taichung Tzu Chi Hospital, Department of Ophthalmology
Primary Subject Heading:	Ophthalmology
Secondary Subject Heading:	Epidemiology, Health services research
Keywords:	OPHTHALMOLOGY, EPIDEMIOLOGY, HEALTH SERVICES ADMINISTRATION & MANAGEMENT

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Prevalence and associated relating factors in patients with hereditary retinal dystrophy---a nationwide population-based study in Taiwan

Peng Yeong Woon[1], Jia-Ying Chien[2], Jen-Hung Wang[3], Yu-Yau Chou[1], Mei-Chen Lin[4, 5], Shun-Ping Huang[1, 2, 6]

[1] Department of Molecular Biology and Human Genetics, Tzu Chi University, Hualien, Taiwan
[2] Institute of Medical Sciences, Tzu Chi University, Hualien, Taiwan
[3]. Department of Medical Research, Tzu Chi General Hospital, Hualien, Taiwan
[4].College of Medicine, China Medical University, Taichung, Taiwan
[5]. Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan
[6].Department of Ophthalmology, Taichung Tzu Chi Hospital, Taichung, Taiwan

Corresponding Author

Shun-Ping Huang
Department of Molecular Biology and Human Genetics,
Tzu Chi University
701, Sec. 3, Chung-Yang Rd, Hualien, 97002, Taiwan
Tel: +886-3-8565301#2694
Fax: +886-3-8561422
E-mail: sphophdoc1688@gms.tcu.edu.tw; sphophdoc1688@gmail.com

Abstract

Objective To investigate the prevalence, incidence and relating factors that are associated with hereditary retinal dystrophy in Taiwan from 2000 to 2013.

Design, Setting and Participants This is a nationwide, population-based, retrospective case-control study using National Health Insurance Database. Study groups are patients with hereditary retinal dystrophies (HRD) as case group; age-matched patients without any diagnosis of HRD as control group. We enrolled 2,418 study subjects, of which 403 were HRD patients. Important relating factors such as hypertension, diabetes, coronary artery disease, autoimmune disease, cancer, liver cirrhosis, chronic kidney disease, stroke, hyperlipidemia, asthma, depression and dementia are also included.

Exposure Patients diagnosed with hereditary retinal dystrophy were retrieved from National Health Insurance Database.

Main outcomes and Measures Odds ratio calculated between the -relating factors and HRD for objects and stratified by age and sex group between 2000 and 2013.

Results Four hundred and three patients were included in the study group and 2015 in the control group. The incidence of HRD was 3.29/100, 000, and prevalence of HRD was 40.5/100,000 persons. The tendency of study group to have more cataract, cystoid macula edema (CME) as compared to the control group. Among the subgroup with comorbidities, the relating factors such as hypertension, diabetes and chronic kidney disease was significantly higher among HRD patients with age 55 and above.

Conclusions 74% of the diagnosed HRD are retinitis pigmentosa. Population based data suggested an increased incidence of cataract in younger patients, whereas older HRD patients are more susceptible to develop CME. Further work is needed to elucidate the mechanism between these ophthalmologic disorders and HRD.

Strengths and limitation of this study

- We conducted a nationwide, population-based study to explore the prevalence, incidence and -relating factors associated with hereditary retinal dystrophy in Taiwan
- Our study suggested an increased incidence of cataract in younger hereditary retinal dystrophy patients whereas older patients are more susceptible to develop cystoid macular edema.
- Younger patients with hereditary retinal dystrophy have a higher incidence to develop hypertension, diabetes and chronic kidney diseases.
- We recommended that regular screening and monitoring of HRD patients

with optical coherence tomography (OCT), blood pressure, levels of electrolytes and serum glucose levels may beneficial for early intervention of patients with HRD and may help to maintain central vision and may prevent vascular, metabolic and renal comorbidities.

1. Introduction

Hereditary retinal dystrophies (HRD), such as retinitis pigmentosa (RP), Cone dystrophy, Stargardt disease, Usher syndrome, Leber's congenital amaurosis, retinoschisis, etc., are a group of genetic retinal disorders exhibiting both genetic and phenotypic heterogeneity with a collectively estimated incidence of 1:2000 to 1:3000[1-3]. Among HRD, retinitis pigmentosa, one of the most common forms with variable clinical manifestations, affects approximately 1 in 3000 to 4000 people worldwide[4, 5].

To date, there is more than 271 genes (Retnet: https://sph.uth.edu/retnet/, last update January 21, 2021) associated with HRD have been identified. The clinical manifestations of HRD patients may vary according to complexity of the genetic background and most common features include night blindness, constricted visual field, color vision deficiency or even total blindness. The other ocular complications such as cataract, cystoid macular edema (CME), or epiretinal membrane, will further deteriorate central vision and increase activity limitation at younger age. A wide range prevalence of these complications in HRD has been reported in different studies. Accurate assessment will help to identify these complications and foster the development of advanced therapeutic approaches.

The aim of this study is to explore the prevalence and relating factors that are associated with HRD in a nationwide, population-based, retrospective case-control study using Taiwan National Health Insurance (NHI) Database. The NHI database was used to retrieve cases of HRD to investigate the events of cataract, CME, epiretinal membrane, retinoschisis and other covariates.

Materials and Methods

Data source

This was a nationwide population-based retrospective case-control study. The National Health Insurance (NHI) program, which was implemented in Taiwan on March 1, 1995, constructed a high coverage health database, named National Health Insurance Database (NHIRD) and enrolled over 99% of population in Taiwan as of today. The records of outpatients, hospitalization, medical treatment, and other medical services of each hospital visit were included in the database. We conducted the analysis by using Longitudinal Health Insurance Database 2000 (LHID 2000), the subset of NHIRD. LHID 2000 consisted of 1 million study subjects, which was randomly sampled from NHIRD and made sure they were already insured in the year 2000. The database was merely for medical research and the identification numbers of all individuals were encrypted to protect the privacy of the individuals. The diagnoses in Taiwan NHIRD are defined according to the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM). The study was approved by the Research Ethics Committee of China Medical University and Hospital in Taiwan (CMUH-104-REC2-115-R4).

Study subjects

We identified 403 subjects from the LHID2000 with the diagnosis of hereditary retinal dystrophies (HRD) (ICD-9-CM Code 362.7x) made between 1 January 2000 and 31 December 2013. The index date for a HRD subject was the date when the disease was first coded.

Control Group

Control patients were defined as subjects without any diagnosis of HRD and were pair matched to the subjects with HRD by age, sex, and index date in a ratio of 5 controls to each HRD subject.

Relating factors and other covariates

The relating factors included cataract (ICD-9: 366.X or Pseudophakia (V43.1) or procedure code: 86007C, 86008C, 86009C, 86010B), cystoid macular edema (ICD-9: 362.53), retinoschisis (ICD-9:361.1), epiretinal membrane (ICD-9: 362.56), retinal detachment (ICD-9: 361.0), and YAG capsulotomy (procedure code: 60013C, 60014C), which had diagnosis record within 1 year

before the index date. Some comorbidities were included as other covariates. These comorbidities were important relating factors in this study. We defined the comorbidities occurred one year before the index date and with at least twice outpatients or once hospitalization record. Hypertension (ICD-9: 401-405, A260, A269), diabetes (ICD-9: 250, A181), coronary artery disease (ICD-9: 410-414, A270, A279), autoimmune disease (ICD-9: 710, 714), cancer (ICD-9: 140-208), liver cirrhosis (ICD-9: 571.2, 571.5, 571.6), chronic kidney disease (ICD-9: 582, 583, 585, 586, 588), stroke (ICD-9: 430-438), hyperlipidemia (ICD-9: 272, A182), asthma (ICD-9: 493), depression (ICD-9: 296.2, 296.3, 296.82, 300.4, 309.0, 309.1, 309.28, 311) and dementia (ICD-9: 290, 294.1, 331.0) were also included.

Statistical analysis

The annual incidence rate of HRD was calculated by the annual newly diagnosed HRD patients divided by every 100,000 person-year. The difference of demographic and comorbidities between two groups was compared by chi-square/ Fisher exact test and t-test for categorical and continuous variable, respectively and the variants/factors of HRD was evaluated by conditional logistic regression and shown by odds ratio (OR), adjusted odds ratio (aOR) and 95% confidence interval (95% C.I.). All statistical analyses were carried out using Statistical Analysis Software (SAS), version 9.4 (SAS Institute Inc., Cary, NC, United States). The significant criteria set at two side p-value less than 0.05.

Patient and Public Involvement

No patient involved

Results

HRD incidence

Figure 1 presented the annual incidence rate of HRD from 2000 to 2013. The incidence rate of HRD showed approximately 2.62-4.55 every 100,000 person-year, with an average rate of approximately 3.29 every 100, 000 person-year in Taiwan. The annual incidence rate was consistent during the 14 years follow up.

Demographics

Figure 2 presented the demographic, relating factors and comorbidities of study subjects. In total we enrolled 2,418 study subjects, including 403 HRD patients and 2,015 non-HRD patients, and the mean age was 49 years old. After comparing the prevalence of relating factors and between HRD and non-HRD group, HRD patients showed significant higher prevalence of cataract ($p<0.001$), CME ($p<0.001$), posterior capsulotomy ($p=0.035$), hypertension ($p=0.016$), diabetes ($p<0.001$), chronic kidney disease ($p=0.013$) and hyperlipidemia than non-HRD patients. Retinitis pigmentosa accounted for 74% of HRD diagnosis.

Factors associated with HRD

Figure 3 revealed the crude and adjusted odds ratio of having HRD for subjects with or without some ocular diseases or comorbidity with the adjustment for age, sex and comorbid diseases. Patients with HRD were significantly associated with cataract (aOR=6.03, 95% CI=3.60-10.10) and CME (aOR=14.64, 95% CI=6.78-31.60), but not with epiretinal membrane, retinal detachment, depression or dementia. The development of CME in HRD patients is correlated to age. The prevalence rate of CME in HRD patients older than 55 years (9.4%) is higher than the HRD patients below 55 years of age (4.5%).

Stratification analysis

Figure 4-1 and 4-2 showed the characteristics of patients with or without HRD stratified by age. Among subjects who were older than 55 years, HRD group had significant higher prevalence of cataract ($p=0.002$), CME ($p<0.001$), diabetes ($p<0.001$) and hyperlipidemia ($p=0.028$). Similarly, HRD group had significant higher prevalence of cataract ($p<0.001$), CME ($p<0.001$), posterior capsulotomy ($p=0.005$), hypertension ($p=0.001$), diabetes ($p=0.035$) and chronic kidney disease ($p=0.017$) among subjects who younger than 55 years old.

After stratification by age and gender, patients who were male (aOR=7.00, 95% CI=3.37-14.54), female (aOR=5.22, 95% CI=2.47-11.05), younger (aOR=22.01, 95% CI=7.86-61.65) or older than 55 years (aOR=3.08, 95% CI=1.55-6.11) with cataract showed significant association with HRD, aOR was higher especially among patients younger than 55 years old (Figure 5). CME also showed significant association with HRD among male (aOR=14.89, 95% CI=5.21-42.60), female (aOR=14.77, 95% CI=4.73-46.06) and patients who are older than 55 years (aOR=8.07, 95% CI=3.43-19.03).

Discussions:

In this retrospective case control study using NHI database, the prevalence of cataract, CME, epiretinal membrane, retinal detachment and retinoschisis in HRD patients (n=403) was 8.2%, 6.5%, 0.5%, 0.5% and 0.3% respectively. Compared with individuals without HRD, patients with HRD had a higher incidence of cataract (8.2% vs 1.5%, p<0.001) and CME (6.5% vs 0.5 %, p<0.001) and HRD patients aged younger than 55 years had an increased risk of hypertension, diabetes and chronic kidney disease. These data indicate the prevalence of potentially treatable HRD related ocular complications is relatively high and the comorbidities are more likely to develop at younger HRD patients.

The reported prevalence of CME in patient with HRD especially RP ranges from 14% to 23 % as evaluated by fluorescein angiography (FA)[6-8], 7.5% to 49% as evaluated by time domain OCT (TD-OCT)[9-12] and 12.5% to 58.6%[13-18] as evaluated by spectral domain OCT (SD-OCT). However, these reports mostly were single-hospital study and were non-population-based data which cannot be used to calculate the exact prevalence rate of CME. Our prevalence for CME (6.5%) is relatively lower than the previous reports but similar to the studies by Oishi et al[11]., detected CME in 49 eyes (7.5%) out of 652 eyes of 326 patients and Hagiwara et al[19]., reported CME was detected in 26 (8%) out of 323 patients with RP using TD-OCT. The big discrepancy in CME prevalence rate among the studies may associated with different definition of CME, different detection methods and equipment or different populations. The exact etiology of CME in HRD remains uncertain and various proposed pathophysiological mechanisms, such as breakdown of the blood-retinal barrier[20, 21], Muller cell dysfunction[22], vitreomacular traction[23, 24], anti-retinal autoantibodies[25], and retinal pigment epithelium dysfunction[26], have been suggested[27, 28]. Additionally, further investigation to evaluate the association between CME and the genetic background effects will also be needed.

Patients with HRD tend to develop cataract at younger age as compared to general population. Posterior subcapsular cataract is the most common form of cataract observed in patients with HRD, whereas nuclear or cortical cataract is more common in age-related cataract. The severity of cataract in HRD patients is related to the onset age and the duration of disease progression. In Taiwan the prevalence rate of cataract surgery was 0.54% and the incidence rate of

first cataract surgery was 0.44% in 2010[29]. Data from previous reports indicated that women had higher incidence rate of cataract surgery [29-33]. In this study, the prevalence rate of cataract surgery is significantly higher in HRD patients compared with age-matched non-HRD people (8.3% vs 1.3%; p<0.001). Adjusted OR of cataract in HRD patients younger than 55 y/o and older than 55 y/o is 22.01 (95% CI=7.86-61.65) and 3.05 (95% CI=1.55-6.11) respectively. Our results suggest that cataract occurred at younger age and more frequently among man than among women in HRD patients (Figure 5).

In this study, HRD subjects younger than 55y/o had a higher prevalence of hypertension, diabetes, and chronic kidney diseases than the age-matched control subjects while HRD subjects older than 55y/o had a higher prevalence of diabetes and hyperlipidemia than the age-matched control subject. The association between these comorbidities and HRD is unclear. Some individuals with HRD may have other associated non-ocular diseases[2, 34]. Patients with Bardet-Biedl syndrome (BBS) [35, 36], Alstrom syndrome (AS)[37, 38], Kearns-Sayre syndrome [39, 40] and Wolfram syndrome[41, 42], have been reported to have the combination of diabetes and retinal dystrophy. BBS and AS patients usually show the symptoms of obesity and impaired renal function while Senior-Loken syndrome patients are not obese but present with severe renal dysfunction[43, 44]. The pathophysiological mechanisms underlying the high prevalence of these comorbidities in HRD patients worth further investigation.

Chen *et al.,*(2021) reported that patients with certain phenotypes such as Leber congenital amaurosis (LCA), retinoschisis (RS), familial exudative vitreoretinopathy (FEVR) and Alstrom syndrome displayed retinal dystrophies earlier in life[45], and probands with ABCA4, RPGR, RP1L1, and CEP290 mutations sought medical attention at an significantly very young age (age onset 0.89-4.00 years old). As ABCA4 was the single most common disease-causing gene in their cohort (15.2%), echoed the data published from the US cohort (17.3%). Consequently, it would be worth further investigation if HRD patients in our study exhibit the similar event. Of noted, the age onset of our cohort was much older (mean 49.2 year-old, Figure 2). They also observed that patients with retinitis pigmentosa (RP), macular dystrophy (MD) and crystalline dystrophy (BCD) occurred at much older age (age onset ranged from 29.42-36.64) [45]. Unfortunately, other relating factors such as hypertension, diabetes, chronic kidney disease and hyperlipidemia did not receive much attention from Chen *et al.,* (2021). Perhaps worth mentioned was that on average, their cohort

had an age-onset much younger (mean age-onset of 28.17 year-old) as compared to the Taiwan IRD population. The HRD age of onset of our cohort (mean 49.2 year-old, Figure 2) closed to the national record, which made our study unique and truly represented.

The central vision of HRD patients may be compromised not only by primary disease process but also by the complications occurring as the diseases progresses. CME and cataract are the main relating factors of central visual deteriorating in patients with HRD. Those complications may be solved with surgery or medication, resulting in improved anatomical and visual outcomes. On the other hand, visual blood vessel endothelium cells are most sensitive to osmotic changes due to high serum glucose levels. An increase in serum glucose level endorses oxidative stress and the production of excessive free radicals which subsequently damage the visual blood vessels. In addition, an increase in blood pressure will further worsen the visual disease progression.

Limitations

This case-control retrospective study has limitations. First, the NHI database does not provide information regarding personal physical activity, nutrition, lifestyles, body mass index or metabolic profiles affecting the risks of hypertension, hyperlipidemia, diabetes and chronic kidney diseases. Second, the ICD-9-CM codes for the diagnosis of HRD and the comorbid diseases were less precise than the data collected through standardized clinical examination. Furthermore, there is no specific code for each different HRD, such as cone-rod dystrophy, Stargardt diseases, Usher syndrome, Leber's congenital amaurosis and other retinal dystrophy associated syndromes. Third, we may have underestimated the prevalence of CME in HRD subjects since there was no standard criteria to define cystoid macular edema on OCT sans from the NHI database.

Conclusions

These finding from our nationwide, population-based case control study suggests an increased risk of cataract in younger HRD patients, whereas older HRD patients are more susceptible to develop CME. Understanding the pathophysiological mechanisms between these ocular complications and HRD will help to develop effective therapies to improve patients' vision. Furthermore, younger HRD patients have a higher tendency to develop hypertension, diabetes and chronic kidney diseases. We recommended that regular

screening and monitoring of HRD patients with optical coherence tomography (OCT), blood pressure, levels of electrolytes and serum glucose levels may beneficial for early intervention of patients with HRD and may help to maintain central vision and may prevent vascular, metabolic and renal comorbidities.

Data Availability Statement

All data relevant to the study are included in the article

Institutional Review Board (IRB)

This study received the approval from the Research Ethics Committee of China Medical University and Hospital in Taiwan [CMUH-104-REC2-115-(AR4)].

Acknowledgements

Funding/Support: This study was supported in part by Collaborative Grant by Tzu Chi Medical Foundation and Tzu Chi University To: Shun-Ping Huang TCAS-107-02, Taiwan Ministry of Health and Welfare Clinical Trial Center (MOHW109-TDU-B-212-114004), MOST Clinical Trial Consortium for Stroke (MOST 109-2321-B-039-002), Tseng-Lien Lin Foundation, Taichung, Taiwan.
Financial Disclosures: The authors declare no financial support or conflict of interest

Author Contribution:

Conceptualization, SP.H. and JH.W.; methodology, software, validation, and formal analysis, MC.L.; resources, SP.H.; writing—original draft preparation, PY.W., JY.C., JH.W., YY.C. and MC.L..; writing—review and editing, JH.W. and SP.H.; supervision, SP.H; funding acquisition, SP.H. All authors have read and agreed to the published version of the manuscript.

Figure captions

Figure 1. Incidence of HRD from 2000 to 2013

Figure 2. Characteristics of patients with or without HRD

Figure 3. Odds Ratios and 95% Confidence Intervals of HRD associated with eye diseases and comorbidities.

Figure 4.1 Characteristics of patients older than 55 y./o with or without HRD

Figure 4.2 Characteristics of patients younger than 55 y/o with or without HRD

Figure 5. Odds ratio and confidence intervals of HRD in different stratification

References

1. Broadgate S, Yu J, Downes SM, Halford S. Unravelling the genetics of inherited retinal dystrophies: Past, present and future. Progress in retinal and eye research 2017;59:53-96.
2. Hartong DT, Berson EL, Dryja TP. Retinitis pigmentosa. Lancet (London, England) 2006;368:1795-809.
3. Hamel CP. Gene discovery and prevalence in inherited retinal dystrophies. Comptes rendus biologies 2014;337:160-6.
4. Boughman JA, Conneally PM, Nance WE. Population genetic studies of retinitis pigmentosa. American journal of human genetics 1980;32:223-35.
5. Heckenlively JR, Yoser SL, Friedman LH, Oversier JJ. Clinical findings and common symptoms in retinitis pigmentosa. American journal of ophthalmology 1988;105:504-11.
6. Newsome DA. Retinal fluorescein leakage in retinitis pigmentosa. Am J Ophthalmol 1986;101:354-60.
7. Fishman GA, Fishman M, Maggiano J. Macular lesions associated with retinitis pigmentosa. Archives of ophthalmology (Chicago, Ill : 1960) 1977;95:798-803.
8. Fishman GA, Maggiano JM, Fishman M. Foveal lesions seen in retinitis pigmentosa. Archives of ophthalmology (Chicago, Ill : 1960) 1977;95:1993-6.
9. Hirakawa H, Iijima H, Gohdo T, Tsukahara S. Optical coherence tomography of cystoid macular edema associated with retinitis pigmentosa. American journal of ophthalmology 1999;128:185-91.
10. Chung H, Hwang JU, Kim JG, Yoon YH. Optical coherence tomography in the diagnosis and monitoring of cystoid macular edema in patients with retinitis pigmentosa. Retina (Philadelphia, Pa) 2006;26:922-7.
11. Oishi A, Otani A, Sasahara M, et al. Photoreceptor integrity and visual acuity in cystoid macular oedema associated with retinitis pigmentosa. Eye (London, England) 2009;23:1411-6.
12. Adackapara CA, Sunness JS, Dibernardo CW, Melia BM, Dagnelie G. Prevalence of cystoid macular edema and stability in oct retinal thickness in eyes with retinitis pigmentosa during a 48-week lutein trial. Retina (Philadelphia, Pa) 2008;28:103-10.
13. Triolo G, Pierro L, Parodi MB, et al. Spectral domain optical coherence tomography findings in patients with retinitis pigmentosa. Ophthalmic research 2013;50:160-4.
14. Iovino C, Au A, Hilely A, et al. Evaluation of the Choroid in Eyes With Retinitis Pigmentosa and Cystoid Macular Edema. Investigative ophthalmology

& visual science 2019;60:5000-5006.
15. Kim YJ, Joe SG, Lee DH, Lee JY, Kim JG, Yoon YH. Correlations between spectral-domain OCT measurements and visual acuity in cystoid macular edema associated with retinitis pigmentosa. Investigative ophthalmology & visual science 2013;54:1303-9.
16. Hajali M, Fishman GA, Anderson RJ. The prevalence of cystoid macular oedema in retinitis pigmentosa patients determined by optical coherence tomography. The British journal of ophthalmology 2008;92:1065-8.
17. Hajali M, Fishman GA. The prevalence of cystoid macular oedema on optical coherence tomography in retinitis pigmentosa patients without cystic changes on fundus examination. Eye (London, England) 2009;23:915-9.
18. Liew G, Strong S, Bradley P, et al. Prevalence of cystoid macular oedema, epiretinal membrane and cataract in retinitis pigmentosa. Br J Ophthalmol 2019;103:1163-1166.
19. Hagiwara A, Yamamoto S, Ogata K, et al. Macular abnormalities in patients with retinitis pigmentosa: prevalence on OCT examination and outcomes of vitreoretinal surgery. Acta ophthalmologica 2011;89:e122-5.
20. Vinores SA, Kuchle M, Derevjanik NL, et al. Blood-retinal barrier breakdown in retinitis pigmentosa: light and electron microscopic immunolocalization. Histology and histopathology 1995;10:913-23.
21. Spalton DJ, Rahi AH, Bird AC. Immunological studies in retinitis pigmentosa associated with retinal vascular leakage. The British journal of ophthalmology 1978;62:183-7.
22. Makiyama Y, Oishi A, Otani A, et al. Prevalence and spatial distribution of cystoid spaces in retinitis pigmentosa: investigation with spectral domain optical coherence tomography. Retina (Philadelphia, Pa) 2014;34:981-8.
23. Schepens CL, Avila MP, Jalkh AE, Trempe CL. Role of the vitreous in cystoid macular edema. Survey of ophthalmology 1984;28 Suppl:499-504.
24. Takezawa M, Tetsuka S, Kakehashi A. Tangential vitreous traction: a possible mechanism of development of cystoid macular edema in retinitis pigmentosa. Clinical ophthalmology (Auckland, NZ) 2011;5:245-8.
25. Heckenlively JR, Aptsiauri N, Nusinowitz S, Peng C, Hargrave PA. Investigations of antiretinal antibodies in pigmentary retinopathy and other retinal degenerations. Transactions of the American Ophthalmological Society 1996;94:179-200; discussion 200-6.
26. Heckenlively JR, Solish AM, Chant SM, Meyers-Elliott RH. Autoimmunity in hereditary retinal degenerations. II. Clinical studies: antiretinal antibodies and fluorescein angiogram findings. The British journal of ophthalmology

1985;69:758-64.
27. Strong S, Liew G, Michaelides M. Retinitis pigmentosa-associated cystoid macular oedema: pathogenesis and avenues of intervention. The British journal of ophthalmology 2017;101:31-37.
28. Strong SA, Hirji N, Quartilho A, Kalitzeos A, Michaelides M. Retrospective cohort study exploring whether an association exists between spatial distribution of cystoid spaces in cystoid macular oedema secondary to retinitis pigmentosa and response to treatment with carbonic anhydrase inhibitors. The British journal of ophthalmology 2019;103:233-237.
29. Lee JS, Chung CC, Lin KK, Yu KH, Kuo CF, See LC. Time trends in cataract surgery and after-cataract laser capsulotomy in Taiwan: A population-based retrospective cohort study. Int J Surg 2016;36:265-273.
30. Gollogly HE, Hodge DO, St Sauver JL, Erie JC. Increasing incidence of cataract surgery: population-based study. J Cataract Refract Surg 2013;39:1383-9.
31. Semmens JB, Li J, Morlet N, Ng J. Trends in cataract surgery and postoperative endophthalmitis in Western Australia (1980-1998): the Endophthalmitis Population Study of Western Australia. Clin Exp Ophthalmol 2003;31:213-9.
32. Behndig A, Montan P, Stenevi U, Kugelberg M, Lundström M. One million cataract surgeries: Swedish National Cataract Register 1992-2009. J Cataract Refract Surg 2011;37:1539-45.
33. Lundström M, Goh PP, Henry Y, et al. The changing pattern of cataract surgery indications: a 5-year study of 2 cataract surgery databases. Ophthalmology 2015;122:31-8.
34. Verbakel SK, van Huet RAC, Boon CJF, et al. Non-syndromic retinitis pigmentosa. Progress in retinal and eye research 2018;66:157-186.
35. O'Dea D, Parfrey PS, Harnett JD, Hefferton D, Cramer BC, Green J. The importance of renal impairment in the natural history of Bardet-Biedl syndrome. American journal of kidney diseases : the official journal of the National Kidney Foundation 1996;27:776-83.
36. Mujahid S, Hunt KF, Cheah YS, et al. The Endocrine and Metabolic Characteristics of a Large Bardet-Biedl Syndrome Clinic Population. The Journal of clinical endocrinology and metabolism 2018;103:1834-1841.
37. Tsang SH, Aycinena ARP, Sharma T. Ciliopathy: Alstrom Syndrome. Advances in experimental medicine and biology 2018;1085:179-180.
38. Millay RH, Weleber RG, Heckenlively JR. Ophthalmologic and systemic manifestations of Alstrom's disease. American journal of ophthalmology

1986;102:482-90.

39. Boltshauser E, Gauthier G. Diabetes Mellitus in Kearns-Sayre syndrome. American journal of diseases of children (1960) 1978;132:321-2.

40. Finsterer J, Frank M. Diabetes in Kearns-Sayre Syndrome: More Common than Anticipated. Canadian journal of diabetes 2015;39:253.

41. d'Annunzio G, Minuto N, D'Amato E, et al. Wolfram syndrome (diabetes insipidus, diabetes, optic atrophy, and deafness): clinical and genetic study. Diabetes care 2008;31:1743-5.

42. Reschke F, Rohayem J, Maffei P, et al. Collaboration for rare diabetes: understanding new treatment options for Wolfram syndrome. Endocrine 2021;71:626-633.

43. Hildebrandt F, Waldherr R, Kutt R, Brandis M. The nephronophthisis complex: clinical and genetic aspects. The Clinical investigator 1992;70:802-8.

44. Hildebrandt F, Zhou W. Nephronophthisis-associated ciliopathies. Journal of the American Society of Nephrology : JASN 2007;18:1855-71.

45. Chen TC, Huang DS, Lin CW, et al. Genetic characteristics and epidemiology of inherited retinal degeneration in Taiwan. NPJ Genom Med. 2021 Feb 19;6(1):16.

Year	HRD	Total Population Person Years	Annual Incidence Rate per 100,000 person years
2000	42	922354	4.55
2001	29	918184	3.16
2002	33	903289	3.65
2003	28	893619	3.13
2004	34	887334	3.83
2005	28	881009	3.18
2006	29	874763	3.32
2007	29	868228	3.34
2008	26	861413	3.02
2009	24	854379	2.81
2010	24	854379	2.81
2011	22	839714	2.62
2012	30	831452	3.61
2013	25	819168	3.05

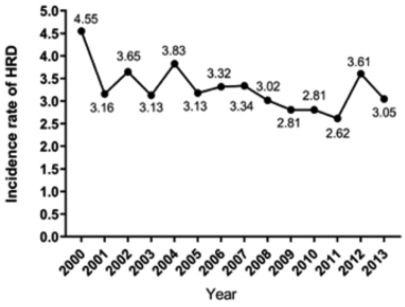


Figure 1. Incidence of HRD from 2000 to 2013

79x52mm (300 x 300 DPI)

Figure 2. Characteristics of patients with or without HRD				
	Total N=2418	Non-HRD (n=2015)	HRD (n=403)	p-value
	n	n (%) / mean(SD)	n (%) / mean(SD)	
Gender				1.000
Female	1242	1035 (51.4)	207 (51.4)	
Male	1176	980 (48.6)	196 (48.6)	
Age, years				1.000
<20	210	175 (8.68)	35 (8.68)	
20-39	552	460 (22.83)	92 (22.83)	
40-59	876	730 (36.23)	146 (36.23)	
≥60	780	650 (32.26)	130 (32.26)	
mean(SD)[a]		49.1 (18.7)	49.2 (18.6)	0.939
Risk factors				
Cataract	64	31 (1.5)	33 (8.2)	<0.001
Macular edema	35	9 (0.5)	26 (6.5)	<0.001
Retinal detachment[b]	4	2 (0.1)	2 (0.5)	0.132
Retinoschisis[b]	1	0 (0.0)	1 (0.3)	0.167
Posterior Capsulotomy	13	8 (0.4)	5 (1.2)	0.035
Epiretinal membrance[b]	3	1 (0.1)	2 (0.5)	0.074
Comorbidity				
Hypertension	471	375 (18.6)	96 (23.8)	0.016
Diabetes	241	176 (8.7)	65 (16.1)	<0.001
Coronary artery disease	127	101 (5)	26 (6.5)	0.237
Autoimmune diseases[b]	1	0 (0)	1 (0.2)	0.167
Malignancies	13	12 (0.6)	1 (0.2)	0.384
Liver cirrhosis	10	9 (0.4)	1 (0.2)	0.571
Chronic kidney disease	34	23 (1.1)	11 (2.7)	0.013
Cerebrovascular disease	98	87 (4.3)	11 (2.7)	0.140
Hyperlipidemia	228	176 (8.7)	52 (12.9)	0.009
Asthma	56	45 (2.2)	11 (2.7)	0.545
Depression	49	38 (1.89)	11 (2.73)	0.273
Dementia	25	22 (1.09)	3 (0.74)	0.529
Retinitis Pigmentosa, RP		-	300 (74.4)	
[a]t-test				
[b]Fisher exact test				

Figure 2. Characteristics of patients with or without HRD

59x81mm (300 x 300 DPI)

Figure 3. Odds Ratios and 95% Confidence Intervals of HRD Associated With eye diseases.				
Characteristics	**OR (95% CI)**	**p value**	**aOR (95% CI)**	**p value**
Cataract				
No	Ref.		Ref.	
Yes	5.68 (3.44-9.40)	<0.001	6.03 (3.60-10.10)	<0.001
Macular edema				
No	Ref.		Ref.	
Yes	14.68 (6.86-31.41)	<0.001	14.64 (6.78-31.60)	<0.001
Retinal detachment				
No	Ref.		Ref.	
Yes	5.00 (0.70-35.50)	0.108	5.15 (0.71-37.38)	0.105
Retinoschisis				
No	Ref.		Ref.	
Yes	-	-	-	-
Posterior Capsulotomy				
No	Ref.		Ref.	
Yes	3.17 (1.03-9.79)	0.045	2.96 (0.90-9.74)	0.074
Epiretinal membrance				
No	Ref.		Ref.	
Yes	8.39 (0.74-94.51)	0.085	-	-
Depression				
No	Ref.		Ref.	
Yes	1.46 (0.74-2.88)	0.276	1.31 (0.65-2.63)	0.449
Dementia				
No	Ref.		Ref.	
Yes	0.65 (0.18-2.31)	0.509	0.76(0.20-2.91)	0.689
Abbreviation: OR, odds ratio; CI, confidence interval				

Figure 3. Odds Ratios and 95% Confidence Intervals of HRD associated with eye diseases and comorbidities.

59x65mm (300 x 300 DPI)

Figure 4-1. Characteristics of patients with or without HRD				
	Total	Non-HRD	HRD	p-value
	n	n (%)	n (%)	
Age, ≧55 years				
Risk factors				
Cataract	40	26 (3.2)	14 (8.7)	0.002
Macular edema	24	9 (1.1)	15 (9.3)	<0.001
Retinal detachment	0	0 (0.0)	0 (0.0)	-
Retinoschisis	3	2 (0.2)	1 (0.6)	0.422
Posterior Capsulotomy	10	8 (1)	2 (1.2)	0.676
Epiretinal membrance	2	0 (0.0)	2 (0.8)	0.028
Comorbidity				
Hypertension	373	305 (37.9)	68 (42.2)	0.301
Diabetes	190	139 (17.3)	51 (31.7)	<0.001
Chronic kidney disease	27	20 (2.5)	7 (4.3)	0.190
Hyperlipidemia	170	132 (16.4)	38 (23.6)	0.028

Figure 4-2. Characteristics of patients with or without HRD				
	Total	Non-HRD	HRD	p-value
	n	n (%)	n (%)	
Age, <55 years				
Risk factors				
Cataract	24	5 (0.4)	19 (7.9)	<0.001
Macular edema	11	0 (0.0)	11 (4.5)	<0.001
Retinal detachment	1	0 (0.0)	1 (0.4)	0.167
Retinoschisis	1	0 (0.0)	1 (0.4)	0.167
Posterior Capsulotomy	3	0 (0.0)	3 (1.2)	0.005
Epiretinal membrance	1	1 (0.1)	0 (0.0)	1.000
Comorbidity				
Hypertension	98	70 (5.8)	28 (11.6)	0.001
Diabetes	51	37 (3.1)	14 (5.8)	0.035
Chronic kidney disease	7	3 (0.2)	4 (1.7)	0.017
Hyperlipidemia	58	44 (3.6)	14 (5.8)	0.119

Figure 4.1 Characteristics of patients older than 55 y./o with or without HRD
Figure 4.2 Characteristics of patients younger than 55 y/o with or without HRD

79x31mm (300 x 300 DPI)

Figure 5. Odds ratio and confidence intervals of HRD in different stratification.				
Variables	**Crude OR (95% CI)**	**p-value**	**Adjusted OR (95% CI)**	**p-value**
Cataract				
Gender				
Female	4.32 (2.10-8.90)	<0.001	5.22 (2.47-11.05)	<0.001
Male	7.40 (3.63-15.09)	<0.001	7.00 (3.37-14.54)	<0.001
Age at baseline				
<55	20.68 (7.60-56.23)	<0.001	22.01 (7.86-61.65)	<0.001
≥55	2.80 (1.44-5.46)	0.002	3.08 (1.55-6.11)	0.001
Macular edema				
Gender				
Female	16.83 (5.45-52.03)	<0.001	14.77 (4.73-46.06)	<0.001
Male	13.00 (4.64-36.47)	<0.001	14.89 (5.21-42.60)	<0.001
Age at baseline				
<55	-		-	
≥55	8.48 (3.70-19.47)	<0.001	8.07 (3.43-19.03)	<0.001

Figure 5. Odds ratio and confidence intervals of HRD in different stratification

59x42mm (300 x 300 DPI)

BMJ Open

Prevalence and associated relating factors in patients with hereditary retinal dystrophy---a nationwide population-based study in Taiwan

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-054111.R2
Article Type:	Original research
Date Submitted by the Author:	28-Feb-2022
Complete List of Authors:	Woon, Peng Yeong; Tzu Chi University, Department of Molecular Biology and Human Genetics Chien, Jia-Ying; Tzu Chi University Wang, Jen-Hung ; Hualien Tzu Chi Medical Center, Department of Medical Research Chou, Yu-Yau; Tzu Chi University, Department of Molecular Biology and Human Genetics Lin, Mei-Chen; China Medical University; China Medical University Hospital Huang, Shun-Ping; Tzu Chi University, Department of Molecular Biology and Human Genetics; Taichung Tzu Chi Hospital, Department of Ophthalmology
Primary Subject Heading:	Ophthalmology
Secondary Subject Heading:	Epidemiology, Health services research
Keywords:	OPHTHALMOLOGY, EPIDEMIOLOGY, HEALTH SERVICES ADMINISTRATION & MANAGEMENT

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Prevalence and associated relating factors in patients with hereditary retinal dystrophy---a nationwide population-based study in Taiwan

Peng Yeong Woon[1], Jia-Ying Chien[2], Jen-Hung Wang[3], Yu-Yau Chou[1], Mei-Chen Lin[4, 5], Shun-Ping Huang[1, 2, 6]

[1] Department of Molecular Biology and Human Genetics, Tzu Chi University, Hualien, Taiwan
[2] Institute of Medical Sciences, Tzu Chi University, Hualien, Taiwan
[3]. Department of Medical Research, Tzu Chi General Hospital, Hualien, Taiwan
[4].College of Medicine, China Medical University, Taichung, Taiwan
[5]. Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan
[6].Department of Ophthalmology, Taichung Tzu Chi Hospital, Taichung, Taiwan

Corresponding Author

Shun-Ping Huang
Department of Molecular Biology and Human Genetics,
Tzu Chi University
701, Sec. 3, Chung-Yang Rd, Hualien, 97002, Taiwan
Tel: +886-3-8565301#2694
Fax: +886-3-8561422
E-mail: sphophdoc1688@gms.tcu.edu.tw; sphophdoc1688@gmail.com

Abstract

Objective To investigate the prevalence, incidence and relating factors that are associated with hereditary retinal dystrophy in Taiwan from 2000 to 2013.

Design, Setting and Participants This is a nationwide, population-based, retrospective case-control study using National Health Insurance Database. Study groups are patients with hereditary retinal dystrophies (HRD) as case group; age-matched patients without any diagnosis of HRD as control group. We enrolled 2,418 study subjects, of which 403 were HRD patients. Important relating factors such as hypertension, diabetes, coronary artery disease, autoimmune disease, cancer, liver cirrhosis, chronic kidney disease, stroke, hyperlipidemia, asthma, depression and dementia are also included.

Exposure Patients diagnosed with hereditary retinal dystrophy were retrieved from National Health Insurance Database.

Main outcomes and Measures Odds ratio calculated between the -relating factors and HRD for objects and stratified by age and sex group between 2000 and 2013.

Results Four hundred and three patients were included in the study group and 2015 in the control group. The incidence of HRD was 3.29/100, 000, and prevalence of HRD was 40.5/100,000 persons. The tendency of study group to have more cataract, cystoid macula edema (CME) as compared to the control group. Among the subgroup with comorbidities, the relating factors such as hypertension, diabetes and chronic kidney disease was significantly higher among HRD patients with age 55 and above.

Conclusions 74% of the diagnosed HRD are retinitis pigmentosa. Population based data suggested an increased incidence of cataract in younger patients, whereas older HRD patients are more susceptible to develop CME. Further work is needed to elucidate the mechanism between these ophthalmologic disorders and HRD.

Strengths and limitation of this study

- We conducted a nationwide, population-based study to explore the prevalence, incidence and -relating factors associated with hereditary retinal dystrophy in Taiwan
- Our study suggested an increased incidence of cataract in younger hereditary retinal dystrophy patients whereas older patients are more susceptible to develop cystoid macular edema.
- Younger patients with hereditary retinal dystrophy have a higher incidence to develop hypertension, diabetes and chronic kidney diseases.
- We recommended that regular screening and monitoring of HRD patients

with optical coherence tomography (OCT), blood pressure, levels of electrolytes and serum glucose levels may beneficial for early intervention of patients with HRD and may help to maintain central vision and may prevent vascular, metabolic and renal comorbidities.

1. Introduction

Hereditary retinal dystrophies (HRD), such as retinitis pigmentosa (RP), Cone dystrophy, Stargardt disease, Usher syndrome, Leber's congenital amaurosis, retinoschisis, etc., are a group of genetic retinal disorders exhibiting both genetic and phenotypic heterogeneity with a collectively estimated incidence of 1:2000 to 1:3000[1-3]. Among HRD, retinitis pigmentosa, one of the most common forms with variable clinical manifestations, affects approximately 1 in 3000 to 4000 people worldwide[4, 5].

To date, there is more than 271 genes (Retnet: https://sph.uth.edu/retnet/, last update January 21, 2021) associated with HRD have been identified. The clinical manifestations of HRD patients may vary according to complexity of the genetic background and most common features include night blindness, constricted visual field, color vision deficiency or even total blindness. The other ocular complications such as cataract, cystoid macular edema (CME), or epiretinal membrane, will further deteriorate central vision and increase activity limitation at younger age. A wide range prevalence of these complications in HRD has been reported in different studies. Accurate assessment will help to identify these complications and foster the development of advanced therapeutic approaches.

The aim of this study is to explore the prevalence and relating factors that are associated with HRD in a nationwide, population-based, retrospective case-control study using Taiwan National Health Insurance (NHI) Database. The NHI database was used to retrieve cases of HRD to investigate the events of cataract, CME, epiretinal membrane, retinoschisis and other covariates.

Materials and Methods

Data source

This was a nationwide population-based retrospective case-control study. The National Health Insurance (NHI) program, which was implemented in Taiwan on March 1, 1995, constructed a high coverage health database, named National Health Insurance Database (NHIRD) and enrolled over 99% of population in Taiwan as of today. The records of outpatients, hospitalization, medical treatment, and other medical services of each hospital visit were included in the database. We conducted the analysis by using Longitudinal Health Insurance Database 2000 (LHID 2000), the subset of NHIRD. LHID 2000 consisted of 1 million study subjects, which was randomly sampled from NHIRD and made sure they were already insured in the year 2000. The database was merely for medical research and the identification numbers of all individuals were encrypted to protect the privacy of the individuals. The diagnoses in Taiwan NHIRD are defined according to the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM). The study was approved by the Research Ethics Committee of China Medical University and Hospital in Taiwan (CMUH-104-REC2-115-R4).

Study subjects

We identified 403 subjects from the LHID2000 with the diagnosis of hereditary retinal dystrophies (HRD) (ICD-9-CM Code 362.7x) made between 1 January 2000 and 31 December 2013. The index date for a HRD subject was the date when the disease was first coded.

Control Group

Control patients were defined as subjects without any diagnosis of HRD and were pair matched to the subjects with HRD by age, sex, and index date in a ratio of 5 controls to each HRD subject.

Relating factors and other covariates

The relating factors included cataract (ICD-9: 366.X or Pseudophakia (V43.1) or procedure code: 86007C, 86008C, 86009C, 86010B), cystoid macular edema (ICD-9: 362.53), retinoschisis (ICD-9:361.1), epiretinal membrane (ICD-9: 362.56), retinal detachment (ICD-9: 361.0), and YAG capsulotomy (procedure code: 60013C, 60014C), which had diagnosis record within 1 year

before the index date. Some comorbidities were included as other covariates. These comorbidities were important relating factors in this study. We defined the comorbidities occurred one year before the index date and with at least twice outpatients or once hospitalization record. Hypertension (ICD-9: 401-405, A260, A269), diabetes (ICD-9: 250, A181), coronary artery disease (ICD-9: 410-414, A270, A279), autoimmune disease (ICD-9: 710, 714), cancer (ICD-9: 140-208), liver cirrhosis (ICD-9: 571.2, 571.5, 571.6), chronic kidney disease (ICD-9: 582, 583, 585, 586, 588), stroke (ICD-9: 430-438), hyperlipidemia (ICD-9: 272, A182), asthma (ICD-9: 493), depression (ICD-9: 296.2, 296.3, 296.82, 300.4, 309.0, 309.1, 309.28, 311) and dementia (ICD-9: 290, 294.1, 331.0) were also included.

Statistical analysis

The annual incidence rate of HRD was calculated by the annual newly diagnosed HRD patients divided by every 100,000 person-year. The difference of demographic and comorbidities between two groups was compared by chi-square/ Fisher exact test and t-test for categorical and continuous variable, respectively and the variants/factors of HRD was evaluated by conditional logistic regression and shown by odds ratio (OR), adjusted odds ratio (aOR) and 95% confidence interval (95% C.I.). All statistical analyses were carried out using Statistical Analysis Software (SAS), version 9.4 (SAS Institute Inc., Cary, NC, United States). The significant criteria set at two side p-value less than 0.05.

Patient and Public Involvement

No patient involved

Results

HRD incidence

Figure 1 presented the annual incidence rate of HRD from 2000 to 2013. The incidence rate of HRD showed approximately 2.62-4.55 every 100,000 person-year, with an average rate of approximately 3.29 every 100, 000 person-year in Taiwan. The annual incidence rate was consistent during the 14 years follow up.

Demographics

Figure 2 presented the demographic, relating factors and comorbidities of study subjects. In total we enrolled 2,418 study subjects, including 403 HRD patients and 2,015 non-HRD patients, and the mean age was 49 years old. After comparing the prevalence of relating factors and between HRD and non-HRD group, HRD patients showed significant higher prevalence of cataract ($p<0.001$), CME ($p<0.001$), posterior capsulotomy ($p=0.035$), hypertension ($p=0.016$), diabetes ($p<0.001$), chronic kidney disease ($p=0.013$) and hyperlipidemia than non-HRD patients. Retinitis pigmentosa accounted for 74% of HRD diagnosis.

Factors associated with HRD

Figure 3 revealed the crude and adjusted odds ratio of having HRD for subjects with or without some ocular diseases or comorbidity with the adjustment for age, sex and comorbid diseases. Patients with HRD were significantly associated with cataract (aOR=6.03, 95% CI=3.60-10.10) and CME (aOR=14.64, 95% CI=6.78-31.60), but not with epiretinal membrane, retinal detachment, depression or dementia. The development of CME in HRD patients is correlated to age. The prevalence rate of CME in HRD patients older than 55 years (9.4%) is higher than the HRD patients below 55 years of age (4.5%).

Stratification analysis

Figure 4-1 and 4-2 showed the characteristics of patients with or without HRD stratified by age. Among subjects who were older than 55 years, HRD group had significant higher prevalence of cataract ($p=0.002$), CME ($p<0.001$), diabetes ($p<0.001$) and hyperlipidemia ($p=0.028$). Similarly, HRD group had significant higher prevalence of cataract ($p<0.001$), CME ($p<0.001$), posterior capsulotomy ($p=0.005$), hypertension ($p=0.001$), diabetes ($p=0.035$) and chronic kidney disease ($p=0.017$) among subjects who younger than 55 years old.

After stratification by age and gender, patients who were male (aOR=7.00, 95% CI=3.37-14.54), female (aOR=5.22, 95% CI=2.47-11.05), younger (aOR=22.01, 95% CI=7.86-61.65) or older than 55 years (aOR=3.08, 95% CI=1.55-6.11) with cataract showed significant association with HRD, aOR was higher especially among patients younger than 55 years old. CME also showed significant association with HRD among male (aOR=14.89, 95% CI=5.21-42.60), female (aOR=14.77, 95% CI=4.73-46.06) and patients who are older than 55 years (aOR=8.07, 95% CI=3.43-19.03).

Discussions:

In this retrospective case control study using NHI database, the prevalence of cataract, CME, epiretinal membrane, retinal detachment and retinoschisis in HRD patients (n=403) was 8.2%, 6.5%, 0.5%, 0.5% and 0.3% respectively. Compared with individuals without HRD, patients with HRD had a higher incidence of cataract (8.2% vs 1.5%, p<0.001) and CME (6.5% vs 0.5 %, p<0.001) and HRD patients aged younger than 55 years had an increased risk of hypertension, diabetes and chronic kidney disease. These data indicate the prevalence of potentially treatable HRD related ocular complications is relatively high and the comorbidities are more likely to develop at younger HRD patients.

The reported prevalence of CME in patient with HRD especially RP ranges from 14% to 23 % as evaluated by fluorescein angiography (FA)[6-8], 7.5% to 49% as evaluated by time domain OCT (TD-OCT)[9-12] and 12.5% to 58.6%[13-18] as evaluated by spectral domain OCT (SD-OCT). However, these reports mostly were single-hospital study and were non-population-based data which cannot be used to calculate the exact prevalence rate of CME. Our prevalence for CME (6.5%) is relatively lower than the previous reports but similar to the studies by Oishi et al[11]., detected CME in 49 eyes (7.5%) out of 652 eyes of 326 patients and Hagiwara et al[19]., reported CME was detected in 26 (8%) out of 323 patients with RP using TD-OCT. The big discrepancy in CME prevalence rate among the studies may associated with different definition of CME, different detection methods and equipment or different populations. The exact etiology of CME in HRD remains uncertain and various proposed pathophysiological mechanisms, such as breakdown of the blood-retinal barrier[20, 21], Muller cell dysfunction[22], vitreomacular traction[23, 24], anti-retinal autoantibodies[25], and retinal pigment epithelium dysfunction[26], have been suggested[27, 28]. Additionally, further investigation to evaluate the association between CME and the genetic background effects will also be needed.

Patients with HRD tend to develop cataract at younger age as compared to general population. Posterior subcapsular cataract is the most common form of cataract observed in patients with HRD, whereas nuclear or cortical cataract is more common in age-related cataract. The severity of cataract in HRD patients is related to the onset age and the duration of disease progression. In Taiwan the prevalence rate of cataract surgery was 0.54% and the incidence rate of

first cataract surgery was 0.44% in 2010[29]. Data from previous reports indicated that women had higher incidence rate of cataract surgery [29-33]. In this study, the prevalence rate of cataract surgery is significantly higher in HRD patients compared with age-matched non-HRD people (8.3% vs 1.3%; p<0.001). Adjusted OR of cataract in HRD patients younger than 55 y/o and older than 55 y/o is 22.01 (95% CI=7.86-61.65) and 3.05 (95% CI=1.55-6.11) respectively. Our results suggest that cataract occurred at younger age and more frequently among man than among women in HRD patients.

In this study, HRD subjects younger than 55y/o had a higher prevalence of hypertension, diabetes, and chronic kidney diseases than the age-matched control subjects while HRD subjects older than 55y/o had a higher prevalence of diabetes and hyperlipidemia than the age-matched control subject. The association between these comorbidities and HRD is unclear. Some individuals with HRD may have other associated non-ocular diseases[2, 34]. Patients with Bardet-Biedl syndrome (BBS) [35, 36], Alstrom syndrome (AS)[37, 38], Kearns-Sayre syndrome [39, 40] and Wolfram syndrome[41, 42], have been reported to have the combination of diabetes and retinal dystrophy. BBS and AS patients usually show the symptoms of obesity and impaired renal function while Senior-Loken syndrome patients are not obese but present with severe renal dysfunction[43, 44]. Several reports have suggested that patients with RP may lower their risk of developing proliferative diabetic retinopathy (PDR). Reducing retinal metabolism may be associated with decreased retina oxygen demand and retinal hypoxia resulting in ameliorating diabetic retinopathy[45,46]. Although retinitis pigmentosa might lack the risk of PDR, the vasoregression in an early stage of diabetic retinopathy and PDR indicated that increased ROS, VEGF, and angiopoietin-2 might induce the progressive degeneration of the blood vessels[47]. The vasoregression of the pathophysiological process between diabetic retinopathy in the early stage is similar to retinitis pigmentosa, suggesting diabetic retinopathy might be enhanced the process of retinitis pigmentosa [48]. Furthermore, patients have retinitis pigmentosa with diabetic retinopathy have been observed in case reports[49-51]. The pathophysiological mechanisms underlying the high prevalence of these comorbidities in HRD patients are worth further investigation.

Chen *et al.,* reported that patients with certain phenotypes such as Leber congenital amaurosis (LCA), retinoschisis (RS), familial exudative vitreoretinopathy (FEVR) and Alstrom syndrome displayed retinal dystrophies

earlier in life[52], and probands with ABCA4, RPGR, RP1L1, and CEP290 mutations sought medical attention at a significantly very young age (age onset 0.89-4.00 years old). As ABCA4 was the single most common disease-causing gene in their cohort (15.2%), echoed the data published from the US cohort (17.3%). Consequently, it would be worth further investigation if HRD patients in our study exhibit the similar event. Of noted, the age onset of our cohort was much older (mean 49.2 year-old, Figure 2). They also observed that patients with retinitis pigmentosa (RP), macular dystrophy (MD) and crystalline dystrophy (BCD) occurred at much older age (age onset ranged from 29.42-36.64) [52]. Unfortunately, other relating factors such as hypertension, diabetes, chronic kidney disease and hyperlipidemia did not receive much attention from Chen *et al.,*. Perhaps worth mentioned was that on average, their cohort had an age-onset much younger (mean age-onset of 28.17 year-old) as compared to the Taiwan IRD population. The HRD age of onset of our cohort (mean 49.2 year-old, Figure 2) closed to the national record, which made our study unique and truly represented.

The central vision of HRD patients may be compromised not only by primary disease process but also by the complications occurring as the diseases progresses. CME and cataract are the main relating factors of central visual deteriorating in patients with HRD. Those complications may be solved with surgery or medication, resulting in improved anatomical and visual outcomes. The putative environmental factors may also contribute to these comorbidities. It has been reported that environmental enrichment can enhance the survival of photoreceptors in a mouse model. This phenomenon is similar to the environmental enrichment that can stimulate the visual cortex. Patients with retinitis pigmentosa lack physical functioning and increase depression in life[53]. Lack of physical activity enhances the relative contributions of comorbidities and HRD. Increasing physical activity can be effective in obesity reduction of oxidant stress. Those factors might affect the comorbidities and HRD[54, 55]. To encourage the patients to explore the environment, physical exercise and cognitive stimulation might delay retinal degeneration [56].

Limitations

This case-control retrospective study has limitations. First, the NHI database does not provide information regarding personal physical activity, nutrition, lifestyles, body mass index or metabolic profiles affecting the risks of hypertension, hyperlipidemia, diabetes and chronic kidney diseases. Second,

the ICD-9-CM codes for the diagnosis of HRD and the comorbid diseases were less precise than the data collected through standardized clinical examination. Furthermore, there is no specific code for each different HRD, such as cone-rod dystrophy, Stargardt diseases, Usher syndrome, Leber's congenital amaurosis and other retinal dystrophy associated syndromes. Third, we may have underestimated the prevalence of CME in HRD subjects since there was no standard criteria to define cystoid macular edema on OCT sans from the NHI database.

Conclusions

These finding from our nationwide, population-based case control study suggests an increased risk of cataract in younger HRD patients, whereas older HRD patients are more susceptible to develop CME. Understanding the pathophysiological mechanisms between these ocular complications and HRD will help to develop effective therapies to improve patients' vision. Furthermore, younger HRD patients have a higher tendency to develop hypertension, diabetes and chronic kidney diseases. We recommended that regular screening and monitoring of HRD patients with optical coherence tomography (OCT), blood pressure, levels of electrolytes and serum glucose levels may beneficial for early intervention of patients with HRD and may help to maintain central vision and may prevent vascular, metabolic and renal comorbidities.

Data Availability Statement

All data relevant to the study are included in the article

Institutional Review Board (IRB)

This study received the approval from the Research Ethics Committee of China Medical University and Hospital in Taiwan [CMUH-104-REC2-115-(AR4)].

Acknowledgements

Funding/Support: This study was supported in part by Collaborative Grant by Tzu Chi Medical Foundation and Tzu Chi University To: Shun-Ping Huang TCAS-107-02, Taiwan Ministry of Health and Welfare Clinical Trial Center (MOHW109-TDU-B-212-114004), MOST Clinical Trial Consortium for Stroke (MOST 109-2321-B-039-002), Tseng-Lien Lin Foundation, Taichung, Taiwan.

Financial Disclosures: The authors declare no financial support or conflict of interest

Author Contribution:

Conceptualization, SP.H. and JH.W.; methodology, software, validation, and formal analysis, MC.L.; resources, SP.H.; writing—original draft preparation, PY.W., JY.C., JH.W., YY.C. and MC.L..; writing—review and editing, JH.W. and SP.H.; supervision, SP.H; funding acquisition, SP.H. All authors have read and agreed to the published version of the manuscript.

Figure captions

Figure 1. Incidence of HRD from 2000 to 2013

Figure 2. Characteristics of patients with or without HRD

Figure 3. Odds Ratios and 95% Confidence Intervals of HRD associated with eye diseases and comorbidities.

Figure 4.1 Characteristics of patients older than 55 y./o with or without HRD

Figure 4.2 Characteristics of patients younger than 55 y/o with or without HRD

References

1. Broadgate S, Yu J, Downes SM, Halford S. Unravelling the genetics of inherited retinal dystrophies: Past, present and future. Progress in retinal and eye research 2017;59:53-96.
2. Hartong DT, Berson EL, Dryja TP. Retinitis pigmentosa. Lancet (London, England) 2006;368:1795-809.
3. Hamel CP. Gene discovery and prevalence in inherited retinal dystrophies. Comptes rendus biologies 2014;337:160-6.
4. Boughman JA, Conneally PM, Nance WE. Population genetic studies of retinitis pigmentosa. American journal of human genetics 1980;32:223-35.
5. Heckenlively JR, Yoser SL, Friedman LH, Oversier JJ. Clinical findings and common symptoms in retinitis pigmentosa. American journal of ophthalmology 1988;105:504-11.
6. Newsome DA. Retinal fluorescein leakage in retinitis pigmentosa. Am J Ophthalmol 1986;101:354-60.
7. Fishman GA, Fishman M, Maggiano J. Macular lesions associated with retinitis pigmentosa. Archives of ophthalmology (Chicago, Ill : 1960) 1977;95:798-803.
8. Fishman GA, Maggiano JM, Fishman M. Foveal lesions seen in retinitis pigmentosa. Archives of ophthalmology (Chicago, Ill : 1960) 1977;95:1993-6.
9. Hirakawa H, Iijima H, Gohdo T, Tsukahara S. Optical coherence tomography of cystoid macular edema associated with retinitis pigmentosa. American journal of ophthalmology 1999;128:185-91.
10. Chung H, Hwang JU, Kim JG, Yoon YH. Optical coherence tomography in the diagnosis and monitoring of cystoid macular edema in patients with retinitis pigmentosa. Retina (Philadelphia, Pa) 2006;26:922-7.
11. Oishi A, Otani A, Sasahara M, et al. Photoreceptor integrity and visual acuity in cystoid macular oedema associated with retinitis pigmentosa. Eye (London, England) 2009;23:1411-6.
12. Adackapara CA, Sunness JS, Dibernardo CW, Melia BM, Dagnelie G. Prevalence of cystoid macular edema and stability in oct retinal thickness in eyes with retinitis pigmentosa during a 48-week lutein trial. Retina (Philadelphia, Pa) 2008;28:103-10.
13. Triolo G, Pierro L, Parodi MB, et al. Spectral domain optical coherence tomography findings in patients with retinitis pigmentosa. Ophthalmic research 2013;50:160-4.
14. Iovino C, Au A, Hilely A, et al. Evaluation of the Choroid in Eyes With Retinitis Pigmentosa and Cystoid Macular Edema. Investigative ophthalmology

& visual science 2019;60:5000-5006.
15. Kim YJ, Joe SG, Lee DH, Lee JY, Kim JG, Yoon YH. Correlations between spectral-domain OCT measurements and visual acuity in cystoid macular edema associated with retinitis pigmentosa. Investigative ophthalmology & visual science 2013;54:1303-9.
16. Hajali M, Fishman GA, Anderson RJ. The prevalence of cystoid macular oedema in retinitis pigmentosa patients determined by optical coherence tomography. The British journal of ophthalmology 2008;92:1065-8.
17. Hajali M, Fishman GA. The prevalence of cystoid macular oedema on optical coherence tomography in retinitis pigmentosa patients without cystic changes on fundus examination. Eye (London, England) 2009;23:915-9.
18. Liew G, Strong S, Bradley P, et al. Prevalence of cystoid macular oedema, epiretinal membrane and cataract in retinitis pigmentosa. Br J Ophthalmol 2019;103:1163-1166.
19. Hagiwara A, Yamamoto S, Ogata K, et al. Macular abnormalities in patients with retinitis pigmentosa: prevalence on OCT examination and outcomes of vitreoretinal surgery. Acta ophthalmologica 2011;89:e122-5.
20. Vinores SA, Kuchle M, Derevjanik NL, et al. Blood-retinal barrier breakdown in retinitis pigmentosa: light and electron microscopic immunolocalization. Histology and histopathology 1995;10:913-23.
21. Spalton DJ, Rahi AH, Bird AC. Immunological studies in retinitis pigmentosa associated with retinal vascular leakage. The British journal of ophthalmology 1978;62:183-7.
22. Makiyama Y, Oishi A, Otani A, et al. Prevalence and spatial distribution of cystoid spaces in retinitis pigmentosa: investigation with spectral domain optical coherence tomography. Retina (Philadelphia, Pa) 2014;34:981-8.
23. Schepens CL, Avila MP, Jalkh AE, Trempe CL. Role of the vitreous in cystoid macular edema. Survey of ophthalmology 1984;28 Suppl:499-504.
24. Takezawa M, Tetsuka S, Kakehashi A. Tangential vitreous traction: a possible mechanism of development of cystoid macular edema in retinitis pigmentosa. Clinical ophthalmology (Auckland, NZ) 2011;5:245-8.
25. Heckenlively JR, Aptsiauri N, Nusinowitz S, Peng C, Hargrave PA. Investigations of antiretinal antibodies in pigmentary retinopathy and other retinal degenerations. Transactions of the American Ophthalmological Society 1996;94:179-200; discussion 200-6.
26. Heckenlively JR, Solish AM, Chant SM, Meyers-Elliott RH. Autoimmunity in hereditary retinal degenerations. II. Clinical studies: antiretinal antibodies and fluorescein angiogram findings. The British journal of ophthalmology

1985;69:758-64.
27. Strong S, Liew G, Michaelides M. Retinitis pigmentosa-associated cystoid macular oedema: pathogenesis and avenues of intervention. The British journal of ophthalmology 2017;101:31-37.
28. Strong SA, Hirji N, Quartilho A, Kalitzeos A, Michaelides M. Retrospective cohort study exploring whether an association exists between spatial distribution of cystoid spaces in cystoid macular oedema secondary to retinitis pigmentosa and response to treatment with carbonic anhydrase inhibitors. The British journal of ophthalmology 2019;103:233-237.
29. Lee JS, Chung CC, Lin KK, Yu KH, Kuo CF, See LC. Time trends in cataract surgery and after-cataract laser capsulotomy in Taiwan: A population-based retrospective cohort study. Int J Surg 2016;36:265-273.
30. Gollogly HE, Hodge DO, St Sauver JL, Erie JC. Increasing incidence of cataract surgery: population-based study. J Cataract Refract Surg 2013;39:1383-9.
31. Semmens JB, Li J, Morlet N, Ng J. Trends in cataract surgery and postoperative endophthalmitis in Western Australia (1980-1998): the Endophthalmitis Population Study of Western Australia. Clin Exp Ophthalmol 2003;31:213-9.
32. Behndig A, Montan P, Stenevi U, Kugelberg M, Lundström M. One million cataract surgeries: Swedish National Cataract Register 1992-2009. J Cataract Refract Surg 2011;37:1539-45.
33. Lundström M, Goh PP, Henry Y, et al. The changing pattern of cataract surgery indications: a 5-year study of 2 cataract surgery databases. Ophthalmology 2015;122:31-8.
34. Verbakel SK, van Huet RAC, Boon CJF, et al. Non-syndromic retinitis pigmentosa. Progress in retinal and eye research 2018;66:157-186.
35. O'Dea D, Parfrey PS, Harnett JD, Hefferton D, Cramer BC, Green J. The importance of renal impairment in the natural history of Bardet-Biedl syndrome. American journal of kidney diseases : the official journal of the National Kidney Foundation 1996;27:776-83.
36. Mujahid S, Hunt KF, Cheah YS, et al. The Endocrine and Metabolic Characteristics of a Large Bardet-Biedl Syndrome Clinic Population. The Journal of clinical endocrinology and metabolism 2018;103:1834-1841.
37. Tsang SH, Aycinena ARP, Sharma T. Ciliopathy: Alstrom Syndrome. Advances in experimental medicine and biology 2018;1085:179-180.
38. Millay RH, Weleber RG, Heckenlively JR. Ophthalmologic and systemic manifestations of Alstrom's disease. American journal of ophthalmology

1986;102:482-90.
39. Boltshauser E, Gauthier G. Diabetes Mellitus in Kearns-Sayre syndrome. American journal of diseases of children (1960) 1978;132:321-2.
40. Finsterer J, Frank M. Diabetes in Kearns-Sayre Syndrome: More Common than Anticipated. Canadian journal of diabetes 2015;39:253.
41. d'Annunzio G, Minuto N, D'Amato E, et al. Wolfram syndrome (diabetes insipidus, diabetes, optic atrophy, and deafness): clinical and genetic study. Diabetes care 2008;31:1743-5.
42. Reschke F, Rohayem J, Maffei P, et al. Collaboration for rare diabetes: understanding new treatment options for Wolfram syndrome. Endocrine 2021;71:626-633.
43. Hildebrandt F, Waldherr R, Kutt R, Brandis M. The nephronophthisis complex: clinical and genetic aspects. The Clinical investigator 1992;70:802-8.
44. Hildebrandt F, Zhou W. Nephronophthisis-associated ciliopathies. Journal of the American Society of Nephrology : JASN 2007;18:1855-71.
45. Sternberg, P., Jr., M.B. Landers, 3rd, and M. Wolbarsht, The negative coincidence of retinitis pigmentosa and proliferative diabetic retinopathy. Am J Ophthalmol, 1984. **97**(6): p. 788-9.
46. ARDEN, G.B., The absence of diabetic retinopathy in patients with retinitis pigmentosa: implications for pathophysiology and possible treatment. 2001. **85**(3): p. 366-370.
47. Hammes, H.-P., et al., Angiopoietin-2 causes pericyte dropout in the normal retina: evidence for involvement in diabetic retinopathy. 2004. **53**(4): p. 1104-1110.
48. Chen, Y.-F., et al., Retinitis Pigmentosa Reduces the Risk of Proliferative Diabetic Retinopathy: A Nationwide Population-Based Cohort Study. PLOS ONE, 2012. **7**(9): p. e45189.
49. Furukawa, T., et al., Hereditary muscular atrophy with ataxia, retinitis pigmentosa, and diabetes mellitus. A clinical report of a family. Neurology, 1968. **18**(10): p. 942-7.
50. Preethi, S. and A.R. Rajalakshmi, Proliferative diabetic retinopathy in typical retinitis pigmentosa. BMJ case reports, 2015. **2015**: p. bcr2014208589.
51. Kawaguchi, Y., et al., Retinal and choroidal hyperreflective foci on spectral-domain optical coherence tomographic images in a patient with retinitis pigmentosa accompanied by diabetic retinopathy. American journal of ophthalmology case reports, 2016. **3**: p. 25-30.
52. Chen TC, Huang DS, Lin CW, et al. Genetic characteristics and epidemiology of inherited retinal degeneration in Taiwan. NPJ Genom Med.

2021 Feb 19;6(1):16.

53. Bittner, A.K., et al., Vision test variability in retinitis pigmentosa and psychosocial factors. Optometry and vision science : official publication of the American Academy of Optometry, 2011. **88**(12): p. 1496-1506.

54. Powers, S.K., et al., Exercise-induced oxidative stress: Friend or foe? J Sport Health Sci, 2020. **9**(5): p. 415-425.

55. Cleven, L., et al., The association between physical activity with incident obesity, coronary heart disease, diabetes and hypertension in adults: a systematic review of longitudinal studies published after 2012. BMC Public Health, 2020. **20**(1): p. 726.

56. Barone, I., et al., Environmental enrichment extends photoreceptor survival and visual function in a mouse model of retinitis pigmentosa. PLoS One, 2012. **7**(11): p. e50726

Year	HRD	Total Population Person Years	Annual Incidence Rate per 100,000 person years
2000	42	922354	4.55
2001	29	918184	3.16
2002	33	903289	3.65
2003	28	893619	3.13
2004	34	887334	3.83
2005	28	881009	3.18
2006	29	874763	3.32
2007	29	868228	3.34
2008	26	861413	3.02
2009	24	854379	2.81
2010	24	854379	2.81
2011	22	839714	2.62
2012	30	831452	3.61
2013	25	819168	3.05

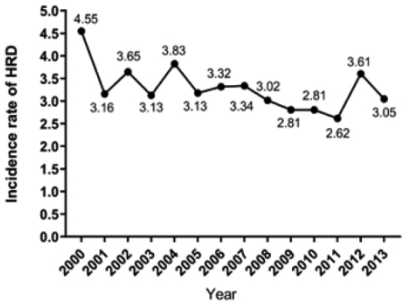


Figure 1. Incidence of HRD from 2000 to 2013

Figure 2. Characteristics of patients with or without HRD				
	Total N=2418	Non-HRD (n=2015)	HRD (n=403)	p-value
	n	n (%) / mean(SD)	n (%) / mean(SD)	
Gender				1.000
Female	1242	1035 (51.4)	207 (51.4)	
Male	1176	980 (48.6)	196 (48.6)	
Age, years				1.000
<20	210	175 (8.68)	35 (8.68)	
20-39	552	460 (22.83)	92 (22.83)	
40-59	876	730 (36.23)	146 (36.23)	
≥60	780	650 (32.26)	130 (32.26)	
mean(SD)[a]		49.1 (18.7)	49.2 (18.6)	0.939
Risk factors				
Cataract	64	31 (1.5)	33 (8.2)	<0.001
Macular edema	35	9 (0.5)	26 (6.5)	<0.001
Retinal detachment[b]	4	2 (0.1)	2 (0.5)	0.132
Retinoschisis[b]	1	0 (0.0)	1 (0.3)	0.167
Posterior Capsulotomy	13	8 (0.4)	5 (1.2)	0.035
Epiretinal membrance[b]	3	1 (0.1)	2 (0.5)	0.074
Comorbidity				
Hypertension	471	375 (18.6)	96 (23.8)	0.016
Diabetes	241	176 (8.7)	65 (16.1)	<0.001
Coronary artery disease	127	101 (5)	26 (6.5)	0.237
Autoimmune diseases[b]	1	0 (0)	1 (0.2)	0.167
Malignancies	13	12 (0.6)	1 (0.2)	0.384
Liver cirrhosis	10	9 (0.4)	1 (0.2)	0.571
Chronic kidney disease	34	23 (1.1)	11 (2.7)	0.013
Cerebrovascular disease	98	87 (4.3)	11 (2.7)	0.140
Hyperlipidemia	228	176 (8.7)	52 (12.9)	0.009
Asthma	56	45 (2.2)	11 (2.7)	0.545
Depression	49	38 (1.89)	11 (2.73)	0.273
Dementia	25	22 (1.09)	3 (0.74)	0.529
Retinitis Pigmentosa, RP		-	300 (74.4)	
[a]t-test				
[b]Fisher exact test				

Figure 2. Characteristics of patients with or without HRD

Figure 3. Odds Ratios and 95% Confidence Intervals of HRD Associated With eye diseases.				
Characteristics	**OR (95% CI)**	**p value**	**aOR (95% CI)**	**p value**
Cataract				
No	Ref.		Ref.	
Yes	5.68 (3.44-9.40)	<0.001	6.03 (3.60-10.10)	<0.001
Macular edema				
No	Ref.		Ref.	
Yes	14.68 (6.86-31.41)	<0.001	14.64 (6.78-31.60)	<0.001
Retinal detachment				
No	Ref.		Ref.	
Yes	5.00 (0.70-35.50)	0.108	5.15 (0.71-37.38)	0.105
Retinoschisis				
No	Ref.		Ref.	
Yes	-	-	-	-
Posterior Capsulotomy				
No	Ref.		Ref.	
Yes	3.17 (1.03-9.79)	0.045	2.96 (0.90-9.74)	0.074
Epiretinal membrance				
No	Ref.		Ref.	
Yes	8.39 (0.74-94.51)	0.085	-	-
Depression				
No	Ref.		Ref.	
Yes	1.46 (0.74-2.88)	0.276	1.31 (0.65-2.63)	0.449
Dementia				
No	Ref.		Ref.	
Yes	0.65 (0.18-2.31)	0.509	0.76(0.20-2.91)	0.689
Abbreviation: OR, odds ratio; CI, confidence interval				

Figure 3. Odds Ratios and 95% Confidence Intervals of HRD associated with eye diseases and comorbidities.

Figure 4-1. Characteristics of patients with or without HRD

	Total	Non-HRD	HRD	p-value
	n	n (%)	n (%)	
Age, ≧55 years				
Risk factors				
Cataract	40	26 (3.2)	14 (8.7)	0.002
Macular edema	24	9 (1.1)	15 (9.3)	<0.001
Retinal detachment	0	0 (0.0)	0 (0.0)	-
Retinoschisis	3	2 (0.2)	1 (0.6)	0.422
Posterior Capsulotomy	10	8 (1)	2 (1.2)	0.676
Epiretinal membrance	2	0 (0.0)	2 (0.8)	0.028
Comorbidity				
Hypertension	373	305 (37.9)	68 (42.2)	0.301
Diabetes	190	139 (17.3)	51 (31.7)	<0.001
Chronic kidney disease	27	20 (2.5)	7 (4.3)	0.190
Hyperlipidemia	170	132 (16.4)	38 (23.6)	0.028

Figure 4-2. Characteristics of patients with or without HRD

	Total	Non-HRD	HRD	p-value
	n	n (%)	n (%)	
Age, <55 years				
Risk factors				
Cataract	24	5 (0.4)	19 (7.9)	<0.001
Macular edema	11	0 (0.0)	11 (4.5)	<0.001
Retinal detachment	1	0 (0.0)	1 (0.4)	0.167
Retinoschisis	1	0 (0.0)	1 (0.4)	0.167
Posterior Capsulotomy	3	0 (0.0)	3 (1.2)	0.005
Epiretinal membrance	1	1 (0.1)	0 (0.0)	1.000
Comorbidity				
Hypertension	98	70 (5.8)	28 (11.6)	0.001
Diabetes	51	37 (3.1)	14 (5.8)	0.035
Chronic kidney disease	7	3 (0.2)	4 (1.7)	0.017
Hyperlipidemia	58	44 (3.6)	14 (5.8)	0.119

Figure 4.1 Characteristics of patients older than 55 y./o with or without HRD
Figure 4.2 Characteristics of patients younger than 55 y/o with or without HRD

BMJ Open

Prevalence and associated relating factors in patients with hereditary retinal dystrophy---a nationwide population-based study in Taiwan

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-054111.R3
Article Type:	Original research
Date Submitted by the Author:	19-Mar-2022
Complete List of Authors:	Woon, Peng Yeong; Tzu Chi University, Department of Molecular Biology and Human Genetics Chien, Jia-Ying; Tzu Chi University Wang, Jen-Hung ; Hualien Tzu Chi Medical Center, Department of Medical Research Chou, Yu-Yau; Tzu Chi University, Department of Molecular Biology and Human Genetics Lin, Mei-Chen; China Medical University; China Medical University Hospital Huang, Shun-Ping; Tzu Chi University, Department of Molecular Biology and Human Genetics; Taichung Tzu Chi Hospital, Department of Ophthalmology
Primary Subject Heading:	Ophthalmology
Secondary Subject Heading:	Epidemiology, Health services research
Keywords:	OPHTHALMOLOGY, EPIDEMIOLOGY, HEALTH SERVICES ADMINISTRATION & MANAGEMENT

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Prevalence and associated relating factors in patients with hereditary retinal dystrophy---a nationwide population-based study in Taiwan

Peng Yeong Woon[1], Jia-Ying Chien[2], Jen-Hung Wang[3], Yu-Yau Chou[1], Mei-Chen Lin[4, 5], Shun-Ping Huang[1, 2, 6]

[1] Department of Molecular Biology and Human Genetics, Tzu Chi University, Hualien, Taiwan
[2] Institute of Medical Sciences, Tzu Chi University, Hualien, Taiwan
[3]. Department of Medical Research, Tzu Chi General Hospital, Hualien, Taiwan
[4].College of Medicine, China Medical University, Taichung, Taiwan
[5]. Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan
[6].Department of Ophthalmology, Taichung Tzu Chi Hospital, Taichung, Taiwan

Corresponding Author

Shun-Ping Huang
Department of Molecular Biology and Human Genetics,
Tzu Chi University
701, Sec. 3, Chung-Yang Rd, Hualien, 97002, Taiwan
Tel: +886-3-8565301#2694
Fax: +886-3-8561422
E-mail: sphophdoc1688@gms.tcu.edu.tw; sphophdoc1688@gmail.com

Abstract

Objective To investigate the prevalence, incidence and relating factors that are associated with hereditary retinal dystrophy in Taiwan from 2000 to 2013.

Design, Setting and Participants This is a nationwide, population-based, retrospective case-control study using National Health Insurance Database. Study groups are patients with hereditary retinal dystrophies (HRD) as case group; age-matched patients without any diagnosis of HRD as control group. We enrolled 2,418 study subjects, of which 403 were HRD patients. Important relating factors such as hypertension, diabetes, coronary artery disease, autoimmune disease, cancer, liver cirrhosis, chronic kidney disease, stroke, hyperlipidemia, asthma, depression and dementia are also included.

Exposure Patients diagnosed with hereditary retinal dystrophy were retrieved from National Health Insurance Database.

Main outcomes and Measures Odds ratio calculated between the -relating factors and HRD for objects and stratified by age and sex group between 2000 and 2013.

Results Four hundred and three patients were included in the study group and 2015 in the control group. The incidence of HRD was 3.29/100, 000, and prevalence of HRD was 40.5/100,000 persons. The tendency of study group to have more cataract, cystoid macula edema (CME) as compared to the control group. Among the subgroup with comorbidities, the relating factors such as hypertension, diabetes and chronic kidney disease was significantly higher among HRD patients with age 55 and above.

Conclusions 74% of the diagnosed HRD are retinitis pigmentosa. Population based data suggested an increased incidence of cataract in younger patients, whereas older HRD patients are more susceptible to develop CME. Further work is needed to elucidate the mechanism between these ophthalmologic disorders and HRD.

Strengths and limitation of this study

- A nationwide, population-based study was conducted to explore the prevalence, incidence, and -relating factors associated with hereditary retinal dystrophy in Taiwan.
- The Taiwan National Health Insurance Database provides over 20 years of comprehensive and detailed registry and claims data covering over 23 million of Taiwan's population.
- Comprehensive details on regional and country-wide hospitalization, healthcare utilization, disease diagnoses, vaccinations, surgical procedures, and medications of every individual.

- This study takes into account of major relating factors and other covariates.
- The risk of misclassification bias on certain disease phenotypes or diseases identifications may not be completely excluded.

1. Introduction

Hereditary retinal dystrophies (HRD), such as retinitis pigmentosa (RP), Cone dystrophy, Stargardt disease, Usher syndrome, Leber's congenital amaurosis, retinoschisis, etc., are a group of genetic retinal disorders exhibiting both genetic and phenotypic heterogeneity with a collectively estimated incidence of 1:2000 to 1:3000[1-3]. Among HRD, retinitis pigmentosa, one of the most common forms with variable clinical manifestations, affects approximately 1 in 3000 to 4000 people worldwide[4, 5].

To date, there is more than 271 genes (Retnet: https://sph.uth.edu/retnet/, last update January 21, 2021) associated with HRD have been identified. The clinical manifestations of HRD patients may vary according to complexity of the genetic background and most common features include night blindness, constricted visual field, color vision deficiency or even total blindness. The other ocular complications such as cataract, cystoid macular edema (CME), or epiretinal membrane, will further deteriorate central vision and increase activity limitation at younger age. A wide range prevalence of these complications in HRD has been reported in different studies. Accurate assessment will help to identify these complications and foster the development of advanced therapeutic approaches.

The aim of this study is to explore the prevalence and relating factors that are associated with HRD in a nationwide, population-based, retrospective case-control study using Taiwan National Health Insurance (NHI) Database. The NHI database was used to retrieve cases of HRD to investigate the events of cataract, CME, epiretinal membrane, retinoschisis and other covariates.

Materials and Methods

Data source

This was a nationwide population-based retrospective case-control study. The National Health Insurance (NHI) program, which was implemented in Taiwan on March 1, 1995, constructed a high coverage health database, named National Health Insurance Database (NHIRD) and enrolled over 99% of population in Taiwan as of today. The records of outpatients, hospitalization, medical treatment, and other medical services of each hospital visit were included in the database. We conducted the analysis by using Longitudinal Health Insurance Database 2000 (LHID 2000), the subset of NHIRD. LHID 2000 consisted of 1 million study subjects, which was randomly sampled from NHIRD and made sure they were already insured in the year 2000. The database was merely for medical research and the identification numbers of all individuals were encrypted to protect the privacy of the individuals. The diagnoses in Taiwan NHIRD are defined according to the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM). The study was approved by the Research Ethics Committee of China Medical University and Hospital in Taiwan (CMUH-104-REC2-115-R4).

Study subjects

We identified 403 subjects from the LHID2000 with the diagnosis of hereditary retinal dystrophies (HRD) (ICD-9-CM Code 362.7x) made between 1 January 2000 and 31 December 2013. The index date for a HRD subject was the date when the disease was first coded.

Control Group

Control patients were defined as subjects without any diagnosis of HRD and were pair matched to the subjects with HRD by age, sex, and index date in a ratio of 5 controls to each HRD subject.

Relating factors and other covariates

The relating factors included cataract (ICD-9: 366.X or Pseudophakia (V43.1) or procedure code: 86007C, 86008C, 86009C, 86010B), cystoid macular edema (ICD-9: 362.53), retinoschisis (ICD-9:361.1), epiretinal membrane (ICD-9: 362.56), retinal detachment (ICD-9: 361.0), and YAG capsulotomy (procedure code: 60013C, 60014C), which had diagnosis record within 1 year

before the index date. Some comorbidities were included as other covariates. These comorbidities were important relating factors in this study. We defined the comorbidities occurred one year before the index date and with at least twice outpatients or once hospitalization record. Hypertension (ICD-9: 401-405, A260, A269), diabetes (ICD-9: 250, A181), coronary artery disease (ICD-9: 410-414, A270, A279), autoimmune disease (ICD-9: 710, 714), cancer (ICD-9: 140-208), liver cirrhosis (ICD-9: 571.2, 571.5, 571.6), chronic kidney disease (ICD-9: 582, 583, 585, 586, 588), stroke (ICD-9: 430-438), hyperlipidemia (ICD-9: 272, A182), asthma (ICD-9: 493), depression (ICD-9: 296.2, 296.3, 296.82, 300.4, 309.0, 309.1, 309.28, 311) and dementia (ICD-9: 290, 294.1, 331.0) were also included.

Statistical analysis

The annual incidence rate of HRD was calculated by the annual newly diagnosed HRD patients divided by every 100,000 person-year. The difference of demographic and comorbidities between two groups was compared by chi-square/ Fisher exact test and t-test for categorical and continuous variable, respectively and the variants/factors of HRD was evaluated by conditional logistic regression and shown by odds ratio (OR), adjusted odds ratio (aOR) and 95% confidence interval (95% C.I.). All statistical analyses were carried out using Statistical Analysis Software (SAS), version 9.4 (SAS Institute Inc., Cary, NC, United States). The significant criteria set at two side p-value less than 0.05.

Patient and Public Involvement

No patient involved

Results

HRD incidence

Figure 1 presented the annual incidence rate of HRD from 2000 to 2013. The incidence rate of HRD showed approximately 2.62-4.55 every 100,000 person-year, with an average rate of approximately 3.29 every 100, 000 person-year in Taiwan. The annual incidence rate was consistent during the 14 years follow up.

Demographics

Figure 2 presented the demographic, relating factors and comorbidities of study subjects. In total we enrolled 2,418 study subjects, including 403 HRD patients and 2,015 non-HRD patients, and the mean age was 49 years old. After comparing the prevalence of relating factors and between HRD and non-HRD group, HRD patients showed significant higher prevalence of cataract ($p<0.001$), CME ($p<0.001$), posterior capsulotomy ($p=0.035$), hypertension ($p=0.016$), diabetes ($p<0.001$), chronic kidney disease ($p=0.013$) and hyperlipidemia than non-HRD patients. Retinitis pigmentosa accounted for 74% of HRD diagnosis.

Factors associated with HRD

Figure 3 revealed the crude and adjusted odds ratio of having HRD for subjects with or without some ocular diseases or comorbidity with the adjustment for age, sex and comorbid diseases. Patients with HRD were significantly associated with cataract (aOR=6.03, 95% CI=3.60-10.10) and CME (aOR=14.64, 95% CI=6.78-31.60), but not with epiretinal membrane, retinal detachment, depression or dementia. The development of CME in HRD patients is correlated to age. The prevalence rate of CME in HRD patients older than 55 years (9.4%) is higher than the HRD patients below 55 years of age (4.5%).

Stratification analysis

Figure 4-1 and 4-2 showed the characteristics of patients with or without HRD stratified by age. Among subjects who were older than 55 years, HRD group had significant higher prevalence of cataract ($p=0.002$), CME ($p<0.001$), diabetes ($p<0.001$) and hyperlipidemia ($p=0.028$). Similarly, HRD group had significant higher prevalence of cataract ($p<0.001$), CME ($p<0.001$), posterior capsulotomy ($p=0.005$), hypertension ($p=0.001$), diabetes ($p=0.035$) and chronic kidney disease ($p=0.017$) among subjects who younger than 55 years old.

After stratification by age and gender, patients who were male (aOR=7.00, 95% CI=3.37-14.54), female (aOR=5.22, 95% CI=2.47-11.05), younger (aOR=22.01, 95% CI=7.86-61.65) or older than 55 years (aOR=3.08, 95% CI=1.55-6.11) with cataract showed significant association with HRD, aOR was higher especially among patients younger than 55 years old. CME also showed significant association with HRD among male (aOR=14.89, 95% CI=5.21-42.60), female (aOR=14.77, 95% CI=4.73-46.06) and patients who are older than 55 years (aOR=8.07, 95% CI=3.43-19.03).

Discussions:

In this retrospective case control study using NHI database, the prevalence of cataract, CME, epiretinal membrane, retinal detachment and retinoschisis in HRD patients (n=403) was 8.2%, 6.5%, 0.5%, 0.5% and 0.3% respectively. Compared with individuals without HRD, patients with HRD had a higher incidence of cataract (8.2% vs 1.5%, p<0.001) and CME (6.5% vs 0.5 %, p<0.001) and HRD patients aged younger than 55 years had an increased risk of hypertension, diabetes and chronic kidney disease. These data indicate the prevalence of potentially treatable HRD related ocular complications is relatively high and the comorbidities are more likely to develop at younger HRD patients.

The reported prevalence of CME in patient with HRD especially RP ranges from 14% to 23 % as evaluated by fluorescein angiography (FA)[6-8], 7.5% to 49% as evaluated by time domain OCT (TD-OCT)[9-12] and 12.5% to 58.6%[13-18] as evaluated by spectral domain OCT (SD-OCT). However, these reports mostly were single-hospital study and were non-population-based data which cannot be used to calculate the exact prevalence rate of CME. Our prevalence for CME (6.5%) is relatively lower than the previous reports but similar to the studies by Oishi et al[11]., detected CME in 49 eyes (7.5%) out of 652 eyes of 326 patients and Hagiwara et al[19]., reported CME was detected in 26 (8%) out of 323 patients with RP using TD-OCT. The big discrepancy in CME prevalence rate among the studies may associated with different definition of CME, different detection methods and equipment or different populations. The exact etiology of CME in HRD remains uncertain and various proposed pathophysiological mechanisms, such as breakdown of the blood-retinal barrier[20, 21], Muller cell dysfunction[22], vitreomacular traction[23, 24], anti-retinal autoantibodies[25], and retinal pigment epithelium dysfunction[26], have been suggested[27, 28]. Additionally, further investigation to evaluate the association between CME and the genetic background effects will also be needed.

Patients with HRD tend to develop cataract at younger age as compared to general population. Posterior subcapsular cataract is the most common form of cataract observed in patients with HRD, whereas nuclear or cortical cataract is more common in age-related cataract. The severity of cataract in HRD patients is related to the onset age and the duration of disease progression. In Taiwan the prevalence rate of cataract surgery was 0.54% and the incidence rate of

first cataract surgery was 0.44% in 2010[29]. Data from previous reports indicated that women had higher incidence rate of cataract surgery [29-33]. In this study, the prevalence rate of cataract surgery is significantly higher in HRD patients compared with age-matched non-HRD people (8.3% vs 1.3%; p<0.001). Adjusted OR of cataract in HRD patients younger than 55 y/o and older than 55 y/o is 22.01 (95% CI=7.86-61.65) and 3.05 (95% CI=1.55-6.11) respectively. Our results suggest that cataract occurred at younger age and more frequently among man than among women in HRD patients.

In this study, HRD subjects younger than 55y/o had a higher prevalence of hypertension, diabetes, and chronic kidney diseases than the age-matched control subjects while HRD subjects older than 55y/o had a higher prevalence of diabetes and hyperlipidemia than the age-matched control subject. The association between these comorbidities and HRD is unclear. Some individuals with HRD may have other associated non-ocular diseases[2, 34]. Patients with Bardet-Biedl syndrome (BBS) [35, 36], Alstrom syndrome (AS)[37, 38], Kearns-Sayre syndrome [39, 40] and Wolfram syndrome[41, 42], have been reported to have the combination of diabetes and retinal dystrophy. BBS and AS patients usually show the symptoms of obesity and impaired renal function while Senior-Loken syndrome patients are not obese but present with severe renal dysfunction[43, 44]. Several reports have suggested that patients with RP may lower their risk of developing proliferative diabetic retinopathy (PDR). Reducing retinal metabolism may be associated with decreased retina oxygen demand and retinal hypoxia resulting in ameliorating diabetic retinopathy[45,46]. Although retinitis pigmentosa might lack the risk of PDR, the vasoregression in an early stage of diabetic retinopathy and PDR indicated that increased ROS, VEGF, and angiopoietin-2 might induce the progressive degeneration of the blood vessels[47]. The vasoregression of the pathophysiological process between diabetic retinopathy in the early stage is similar to retinitis pigmentosa, suggesting diabetic retinopathy might be enhanced the process of retinitis pigmentosa [48]. Furthermore, patients have retinitis pigmentosa with diabetic retinopathy have been observed in case reports[49-51]. The pathophysiological mechanisms underlying the high prevalence of these comorbidities in HRD patients are worth further investigation.

Chen *et al.,* reported that patients with certain phenotypes such as Leber congenital amaurosis (LCA), retinoschisis (RS), familial exudative vitreoretinopathy (FEVR) and Alstrom syndrome displayed retinal dystrophies

earlier in life[52], and probands with ABCA4, RPGR, RP1L1, and CEP290 mutations sought medical attention at a significantly very young age (age onset 0.89-4.00 years old). As ABCA4 was the single most common disease-causing gene in their cohort (15.2%), echoed the data published from the US cohort (17.3%). Consequently, it would be worth further investigation if HRD patients in our study exhibit the similar event. Of noted, the age onset of our cohort was much older (mean 49.2 year-old, Figure 2). They also observed that patients with retinitis pigmentosa (RP), macular dystrophy (MD) and crystalline dystrophy (BCD) occurred at much older age (age onset ranged from 29.42-36.64) [52]. Unfortunately, other relating factors such as hypertension, diabetes, chronic kidney disease and hyperlipidemia did not receive much attention from Chen *et al.,*. Perhaps worth mentioned was that on average, their cohort had an age-onset much younger (mean age-onset of 28.17 year-old) as compared to the Taiwan IRD population. The HRD age of onset of our cohort (mean 49.2 year-old, Figure 2) closed to the national record, which made our study unique and truly represented.

The central vision of HRD patients may be compromised not only by primary disease process but also by the complications occurring as the diseases progresses. CME and cataract are the main relating factors of central visual deteriorating in patients with HRD. Those complications may be solved with surgery or medication, resulting in improved anatomical and visual outcomes. The putative environmental factors may also contribute to these comorbidities. It has been reported that environmental enrichment can enhance the survival of photoreceptors in a mouse model. This phenomenon is similar to the environmental enrichment that can stimulate the visual cortex. Patients with retinitis pigmentosa lack physical functioning and increase depression in life[53]. Lack of physical activity enhances the relative contributions of comorbidities and HRD. Increasing physical activity can be effective in obesity reduction of oxidant stress. Those factors might affect the comorbidities and HRD[54, 55]. To encourage the patients to explore the environment, physical exercise and cognitive stimulation might delay retinal degeneration [56].

Limitations

This case-control retrospective study has limitations. First, the NHI database does not provide information regarding personal physical activity, nutrition, lifestyles, body mass index or metabolic profiles affecting the risks of hypertension, hyperlipidemia, diabetes and chronic kidney diseases. Second,

the ICD-9-CM codes for the diagnosis of HRD and the comorbid diseases were less precise than the data collected through standardized clinical examination. Furthermore, there is no specific code for each different HRD, such as cone-rod dystrophy, Stargardt diseases, Usher syndrome, Leber's congenital amaurosis and other retinal dystrophy associated syndromes. Third, we may have underestimated the prevalence of CME in HRD subjects since there was no standard criteria to define cystoid macular edema on OCT sans from the NHI database.

Conclusions

These finding from our nationwide, population-based case control study suggests an increased risk of cataract in younger HRD patients, whereas older HRD patients are more susceptible to develop CME. Understanding the pathophysiological mechanisms between these ocular complications and HRD will help to develop effective therapies to improve patients' vision. Furthermore, younger HRD patients have a higher tendency to develop hypertension, diabetes and chronic kidney diseases. We recommended that regular screening and monitoring of HRD patients with optical coherence tomography (OCT), blood pressure, levels of electrolytes and serum glucose levels may beneficial for early intervention of patients with HRD and may help to maintain central vision and may prevent vascular, metabolic and renal comorbidities.

Data Availability Statement

All data relevant to the study are included in the article

Ethics statements

Patient consent for publication

Not applicable. The data source of this study was obtained from pseudonymized (coded) medical data of the National Health Insurance Database (NHIRD) in Taiwan. We conducted the analysis by using the Longitudinal Health Insurance Database 2000 (LHID 2000), the subset of NHIRD. LHID 2000 consisted of 1 million study subjects, which were randomly sampled from NHIRD.

Ethics approval

The data from the National Health Insurance Database (NHIRD) were

anonymized before the authors accessed them for the purpose of this study. This study received the approval from the Research Ethics Committee of China Medical University and Hospital in Taiwan [CMUH-104-REC2-115-(AR4)].

Acknowledgements

Funding/Support: This study was supported in part by Collaborative Grant by Tzu Chi Medical Foundation and Tzu Chi University To: Shun-Ping Huang TCAS-107-02, Taiwan Ministry of Health and Welfare Clinical Trial Center (MOHW109-TDU-B-212-114004), MOST Clinical Trial Consortium for Stroke (MOST 109-2321-B-039-002), Tseng-Lien Lin Foundation, Taichung, Taiwan.
Financial Disclosures: The authors declare no financial support or conflict of interest

Author Contribution:

Conceptualization, SP.H. and JH.W.; methodology, software, validation, and formal analysis, MC.L.; resources, SP.H.; writing—original draft preparation, PY.W., JY.C., JH.W., YY.C. and MC.L..; writing—review and editing, JH.W. and SP.H.; supervision, SP.H; funding acquisition, SP.H. All authors have read and agreed to the published version of the manuscript.

Figure captions

Figure 1. Incidence of HRD from 2000 to 2013

Figure 2. Characteristics of patients with or without HRD

Figure 3. Odds Ratios and 95% Confidence Intervals of HRD associated with eye diseases and comorbidities.

Figure 4.1 Characteristics of patients older than 55 y./o with or without HRD

Figure 4.2 Characteristics of patients younger than 55 y/o with or without HRD

References

1. Broadgate S, Yu J, Downes SM, Halford S. Unravelling the genetics of inherited retinal dystrophies: Past, present and future. Progress in retinal and eye research 2017;59:53-96.
2. Hartong DT, Berson EL, Dryja TP. Retinitis pigmentosa. Lancet (London, England) 2006;368:1795-809.
3. Hamel CP. Gene discovery and prevalence in inherited retinal dystrophies. Comptes rendus biologies 2014;337:160-6.
4. Boughman JA, Conneally PM, Nance WE. Population genetic studies of retinitis pigmentosa. American journal of human genetics 1980;32:223-35.
5. Heckenlively JR, Yoser SL, Friedman LH, Oversier JJ. Clinical findings and common symptoms in retinitis pigmentosa. American journal of ophthalmology 1988;105:504-11.
6. Newsome DA. Retinal fluorescein leakage in retinitis pigmentosa. Am J Ophthalmol 1986;101:354-60.
7. Fishman GA, Fishman M, Maggiano J. Macular lesions associated with retinitis pigmentosa. Archives of ophthalmology (Chicago, Ill : 1960) 1977;95:798-803.
8. Fishman GA, Maggiano JM, Fishman M. Foveal lesions seen in retinitis pigmentosa. Archives of ophthalmology (Chicago, Ill : 1960) 1977;95:1993-6.
9. Hirakawa H, Iijima H, Gohdo T, Tsukahara S. Optical coherence tomography of cystoid macular edema associated with retinitis pigmentosa. American journal of ophthalmology 1999;128:185-91.
10. Chung H, Hwang JU, Kim JG, Yoon YH. Optical coherence tomography in the diagnosis and monitoring of cystoid macular edema in patients with retinitis pigmentosa. Retina (Philadelphia, Pa) 2006;26:922-7.
11. Oishi A, Otani A, Sasahara M, et al. Photoreceptor integrity and visual acuity in cystoid macular oedema associated with retinitis pigmentosa. Eye (London, England) 2009;23:1411-6.
12. Adackapara CA, Sunness JS, Dibernardo CW, Melia BM, Dagnelie G. Prevalence of cystoid macular edema and stability in oct retinal thickness in eyes with retinitis pigmentosa during a 48-week lutein trial. Retina (Philadelphia, Pa) 2008;28:103-10.
13. Triolo G, Pierro L, Parodi MB, et al. Spectral domain optical coherence tomography findings in patients with retinitis pigmentosa. Ophthalmic research 2013;50:160-4.
14. Iovino C, Au A, Hilely A, et al. Evaluation of the Choroid in Eyes With Retinitis Pigmentosa and Cystoid Macular Edema. Investigative ophthalmology

& visual science 2019;60:5000-5006.
15. Kim YJ, Joe SG, Lee DH, Lee JY, Kim JG, Yoon YH. Correlations between spectral-domain OCT measurements and visual acuity in cystoid macular edema associated with retinitis pigmentosa. Investigative ophthalmology & visual science 2013;54:1303-9.
16. Hajali M, Fishman GA, Anderson RJ. The prevalence of cystoid macular oedema in retinitis pigmentosa patients determined by optical coherence tomography. The British journal of ophthalmology 2008;92:1065-8.
17. Hajali M, Fishman GA. The prevalence of cystoid macular oedema on optical coherence tomography in retinitis pigmentosa patients without cystic changes on fundus examination. Eye (London, England) 2009;23:915-9.
18. Liew G, Strong S, Bradley P, et al. Prevalence of cystoid macular oedema, epiretinal membrane and cataract in retinitis pigmentosa. Br J Ophthalmol 2019;103:1163-1166.
19. Hagiwara A, Yamamoto S, Ogata K, et al. Macular abnormalities in patients with retinitis pigmentosa: prevalence on OCT examination and outcomes of vitreoretinal surgery. Acta ophthalmologica 2011;89:e122-5.
20. Vinores SA, Kuchle M, Derevjanik NL, et al. Blood-retinal barrier breakdown in retinitis pigmentosa: light and electron microscopic immunolocalization. Histology and histopathology 1995;10:913-23.
21. Spalton DJ, Rahi AH, Bird AC. Immunological studies in retinitis pigmentosa associated with retinal vascular leakage. The British journal of ophthalmology 1978;62:183-7.
22. Makiyama Y, Oishi A, Otani A, et al. Prevalence and spatial distribution of cystoid spaces in retinitis pigmentosa: investigation with spectral domain optical coherence tomography. Retina (Philadelphia, Pa) 2014;34:981-8.
23. Schepens CL, Avila MP, Jalkh AE, Trempe CL. Role of the vitreous in cystoid macular edema. Survey of ophthalmology 1984;28 Suppl:499-504.
24. Takezawa M, Tetsuka S, Kakehashi A. Tangential vitreous traction: a possible mechanism of development of cystoid macular edema in retinitis pigmentosa. Clinical ophthalmology (Auckland, NZ) 2011;5:245-8.
25. Heckenlively JR, Aptsiauri N, Nusinowitz S, Peng C, Hargrave PA. Investigations of antiretinal antibodies in pigmentary retinopathy and other retinal degenerations. Transactions of the American Ophthalmological Society 1996;94:179-200; discussion 200-6.
26. Heckenlively JR, Solish AM, Chant SM, Meyers-Elliott RH. Autoimmunity in hereditary retinal degenerations. II. Clinical studies: antiretinal antibodies and fluorescein angiogram findings. The British journal of ophthalmology

1985;69:758-64.
27. Strong S, Liew G, Michaelides M. Retinitis pigmentosa-associated cystoid macular oedema: pathogenesis and avenues of intervention. The British journal of ophthalmology 2017;101:31-37.
28. Strong SA, Hirji N, Quartilho A, Kalitzeos A, Michaelides M. Retrospective cohort study exploring whether an association exists between spatial distribution of cystoid spaces in cystoid macular oedema secondary to retinitis pigmentosa and response to treatment with carbonic anhydrase inhibitors. The British journal of ophthalmology 2019;103:233-237.
29. Lee JS, Chung CC, Lin KK, Yu KH, Kuo CF, See LC. Time trends in cataract surgery and after-cataract laser capsulotomy in Taiwan: A population-based retrospective cohort study. Int J Surg 2016;36:265-273.
30. Gollogly HE, Hodge DO, St Sauver JL, Erie JC. Increasing incidence of cataract surgery: population-based study. J Cataract Refract Surg 2013;39:1383-9.
31. Semmens JB, Li J, Morlet N, Ng J. Trends in cataract surgery and postoperative endophthalmitis in Western Australia (1980-1998): the Endophthalmitis Population Study of Western Australia. Clin Exp Ophthalmol 2003;31:213-9.
32. Behndig A, Montan P, Stenevi U, Kugelberg M, Lundström M. One million cataract surgeries: Swedish National Cataract Register 1992-2009. J Cataract Refract Surg 2011;37:1539-45.
33. Lundström M, Goh PP, Henry Y, et al. The changing pattern of cataract surgery indications: a 5-year study of 2 cataract surgery databases. Ophthalmology 2015;122:31-8.
34. Verbakel SK, van Huet RAC, Boon CJF, et al. Non-syndromic retinitis pigmentosa. Progress in retinal and eye research 2018;66:157-186.
35. O'Dea D, Parfrey PS, Harnett JD, Hefferton D, Cramer BC, Green J. The importance of renal impairment in the natural history of Bardet-Biedl syndrome. American journal of kidney diseases : the official journal of the National Kidney Foundation 1996;27:776-83.
36. Mujahid S, Hunt KF, Cheah YS, et al. The Endocrine and Metabolic Characteristics of a Large Bardet-Biedl Syndrome Clinic Population. The Journal of clinical endocrinology and metabolism 2018;103:1834-1841.
37. Tsang SH, Aycinena ARP, Sharma T. Ciliopathy: Alstrom Syndrome. Advances in experimental medicine and biology 2018;1085:179-180.
38. Millay RH, Weleber RG, Heckenlively JR. Ophthalmologic and systemic manifestations of Alstrom's disease. American journal of ophthalmology

1986;102:482-90.
39. Boltshauser E, Gauthier G. Diabetes Mellitus in Kearns-Sayre syndrome. American journal of diseases of children (1960) 1978;132:321-2.
40. Finsterer J, Frank M. Diabetes in Kearns-Sayre Syndrome: More Common than Anticipated. Canadian journal of diabetes 2015;39:253.
41. d'Annunzio G, Minuto N, D'Amato E, et al. Wolfram syndrome (diabetes insipidus, diabetes, optic atrophy, and deafness): clinical and genetic study. Diabetes care 2008;31:1743-5.
42. Reschke F, Rohayem J, Maffei P, et al. Collaboration for rare diabetes: understanding new treatment options for Wolfram syndrome. Endocrine 2021;71:626-633.
43. Hildebrandt F, Waldherr R, Kutt R, Brandis M. The nephronophthisis complex: clinical and genetic aspects. The Clinical investigator 1992;70:802-8.
44. Hildebrandt F, Zhou W. Nephronophthisis-associated ciliopathies. Journal of the American Society of Nephrology : JASN 2007;18:1855-71.
45. Sternberg, P., Jr., M.B. Landers, 3rd, and M. Wolbarsht, The negative coincidence of retinitis pigmentosa and proliferative diabetic retinopathy. Am J Ophthalmol, 1984. **97**(6): p. 788-9.
46. ARDEN, G.B., The absence of diabetic retinopathy in patients with retinitis pigmentosa: implications for pathophysiology and possible treatment. 2001. **85**(3): p. 366-370.
47. Hammes, H.-P., et al., Angiopoietin-2 causes pericyte dropout in the normal retina: evidence for involvement in diabetic retinopathy. 2004. **53**(4): p. 1104-1110.
48. Chen, Y.-F., et al., Retinitis Pigmentosa Reduces the Risk of Proliferative Diabetic Retinopathy: A Nationwide Population-Based Cohort Study. PLOS ONE, 2012. **7**(9): p. e45189.
49. Furukawa, T., et al., Hereditary muscular atrophy with ataxia, retinitis pigmentosa, and diabetes mellitus. A clinical report of a family. Neurology, 1968. **18**(10): p. 942-7.
50. Preethi, S. and A.R. Rajalakshmi, Proliferative diabetic retinopathy in typical retinitis pigmentosa. BMJ case reports, 2015. **2015**: p. bcr2014208589.
51. Kawaguchi, Y., et al., Retinal and choroidal hyperreflective foci on spectral-domain optical coherence tomographic images in a patient with retinitis pigmentosa accompanied by diabetic retinopathy. American journal of ophthalmology case reports, 2016. **3**: p. 25-30.
52. Chen TC, Huang DS, Lin CW, et al. Genetic characteristics and epidemiology of inherited retinal degeneration in Taiwan. NPJ Genom Med.

2021 Feb 19;6(1):16.

53. Bittner, A.K., et al., Vision test variability in retinitis pigmentosa and psychosocial factors. Optometry and vision science : official publication of the American Academy of Optometry, 2011. **88**(12): p. 1496-1506.

54. Powers, S.K., et al., Exercise-induced oxidative stress: Friend or foe? J Sport Health Sci, 2020. **9**(5): p. 415-425.

55. Cleven, L., et al., The association between physical activity with incident obesity, coronary heart disease, diabetes and hypertension in adults: a systematic review of longitudinal studies published after 2012. BMC Public Health, 2020. **20**(1): p. 726.

56. Barone, I., et al., Environmental enrichment extends photoreceptor survival and visual function in a mouse model of retinitis pigmentosa. PLoS One, 2012. **7**(11): p. e50726

Year	HRD	Total Population Person Years	Annual Incidence Rate per 100,000 person years
2000	42	922354	4.55
2001	29	918184	3.16
2002	33	903289	3.65
2003	28	893619	3.13
2004	34	887334	3.83
2005	28	881009	3.18
2006	29	874763	3.32
2007	29	868228	3.34
2008	26	861413	3.02
2009	24	854379	2.81
2010	24	854379	2.81
2011	22	839714	2.62
2012	30	831452	3.61
2013	25	819168	3.05

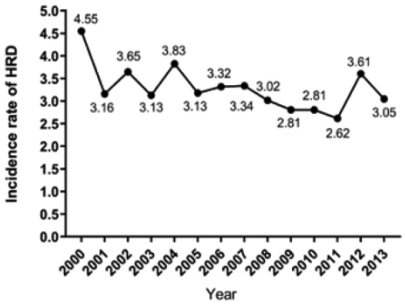


Figure 1. Incidence of HRD from 2000 to 2013

Figure 2. Characteristics of patients with or without HRD				
	Total N=2418	Non-HRD (n=2015)	HRD (n=403)	p-value
	n	n (%) / mean(SD)	n (%) / mean(SD)	
Gender				1.000
Female	1242	1035 (51.4)	207 (51.4)	
Male	1176	980 (48.6)	196 (48.6)	
Age, years				1.000
<20	210	175 (8.68)	35 (8.68)	
20-39	552	460 (22.83)	92 (22.83)	
40-59	876	730 (36.23)	146 (36.23)	
≥60	780	650 (32.26)	130 (32.26)	
mean(SD)[a]		49.1 (18.7)	49.2 (18.6)	0.939
Risk factors				
Cataract	64	31 (1.5)	33 (8.2)	<0.001
Macular edema	35	9 (0.5)	26 (6.5)	<0.001
Retinal detachment[b]	4	2 (0.1)	2 (0.5)	0.132
Retinoschisis[b]	1	0 (0.0)	1 (0.3)	0.167
Posterior Capsulotomy	13	8 (0.4)	5 (1.2)	0.035
Epiretinal membrance[b]	3	1 (0.1)	2 (0.5)	0.074
Comorbidity				
Hypertension	471	375 (18.6)	96 (23.8)	0.016
Diabetes	241	176 (8.7)	65 (16.1)	<0.001
Coronary artery disease	127	101 (5)	26 (6.5)	0.237
Autoimmune diseases[b]	1	0 (0)	1 (0.2)	0.167
Malignancies	13	12 (0.6)	1 (0.2)	0.384
Liver cirrhosis	10	9 (0.4)	1 (0.2)	0.571
Chronic kidney disease	34	23 (1.1)	11 (2.7)	0.013
Cerebrovascular disease	98	87 (4.3)	11 (2.7)	0.140
Hyperlipidemia	228	176 (8.7)	52 (12.9)	0.009
Asthma	56	45 (2.2)	11 (2.7)	0.545
Depression	49	38 (1.89)	11 (2.73)	0.273
Dementia	25	22 (1.09)	3 (0.74)	0.529
Retinitis Pigmentosa, RP		-	300 (74.4)	
[a]t-test				
[b]Fisher exact test				

Figure 2. Characteristics of patients with or without HRD

Figure 3. Odds Ratios and 95% Confidence Intervals of HRD Associated With eye diseases.				
Characteristics	**OR (95% CI)**	**p value**	**aOR (95% CI)**	**p value**
Cataract				
No	Ref.		Ref.	
Yes	5.68 (3.44-9.40)	<0.001	6.03 (3.60-10.10)	<0.001
Macular edema				
No	Ref.		Ref.	
Yes	14.68 (6.86-31.41)	<0.001	14.64 (6.78-31.60)	<0.001
Retinal detachment				
No	Ref.		Ref.	
Yes	5.00 (0.70-35.50)	0.108	5.15 (0.71-37.38)	0.105
Retinoschisis				
No	Ref.		Ref.	
Yes	-	-	-	-
Posterior Capsulotomy				
No	Ref.		Ref.	
Yes	3.17 (1.03-9.79)	0.045	2.96 (0.90-9.74)	0.074
Epiretinal membrance				
No	Ref.		Ref.	
Yes	8.39 (0.74-94.51)	0.085	-	-
Depression				
No	Ref.		Ref.	
Yes	1.46 (0.74-2.88)	0.276	1.31 (0.65-2.63)	0.449
Dementia				
No	Ref.		Ref.	
Yes	0.65 (0.18-2.31)	0.509	0.76(0.20-2.91)	0.689
Abbreviation: OR, odds ratio; CI, confidence interval				

Figure 3. Odds Ratios and 95% Confidence Intervals of HRD associated with eye diseases and comorbidities.

Figure 4-1. Characteristics of patients with or without HRD

	Total	Non-HRD	HRD	p-value
	n	n (%)	n (%)	
Age, ≧55 years				
Risk factors				
Cataract	40	26 (3.2)	14 (8.7)	0.002
Macular edema	24	9 (1.1)	15 (9.3)	<0.001
Retinal detachment	0	0 (0.0)	0 (0.0)	-
Retinoschisis	3	2 (0.2)	1 (0.6)	0.422
Posterior Capsulotomy	10	8 (1)	2 (1.2)	0.676
Epiretinal membrance	2	0 (0.0)	2 (0.8)	0.028
Comorbidity				
Hypertension	373	305 (37.9)	68 (42.2)	0.301
Diabetes	190	139 (17.3)	51 (31.7)	<0.001
Chronic kidney disease	27	20 (2.5)	7 (4.3)	0.190
Hyperlipidemia	170	132 (16.4)	38 (23.6)	0.028

Figure 4-2. Characteristics of patients with or without HRD

	Total	Non-HRD	HRD	p-value
	n	n (%)	n (%)	
Age, <55 years				
Risk factors				
Cataract	24	5 (0.4)	19 (7.9)	<0.001
Macular edema	11	0 (0.0)	11 (4.5)	<0.001
Retinal detachment	1	0 (0.0)	1 (0.4)	0.167
Retinoschisis	1	0 (0.0)	1 (0.4)	0.167
Posterior Capsulotomy	3	0 (0.0)	3 (1.2)	0.005
Epiretinal membrance	1	1 (0.1)	0 (0.0)	1.000
Comorbidity				
Hypertension	98	70 (5.8)	28 (11.6)	0.001
Diabetes	51	37 (3.1)	14 (5.8)	0.035
Chronic kidney disease	7	3 (0.2)	4 (1.7)	0.017
Hyperlipidemia	58	44 (3.6)	14 (5.8)	0.119

Figure 4.1 Characteristics of patients older than 55 y./o with or without HRD
Figure 4.2 Characteristics of patients younger than 55 y/o with or without HRD

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2	4-11
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2	17-28
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4	10-20
Objectives	3	State specific objectives, including any prespecified hypotheses	4	22-26
Methods				
Study design	4	Present key elements of study design early in the paper	4	3-18
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4	21-29
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4	21-24
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	4	27-29
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4; 5	32-36; 1-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5; 6*	*32-36; 1-11*
Bias	9	Describe any efforts to address potential sources of bias	6	14-23
Study size	10	Explain how the study size was arrived at	7	10-18

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7	21-38
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6	14-23
		(*b*) Describe any methods used to examine subgroups and interactions	7	32-38
		(*c*) Explain how missing data were addressed	8	2-9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	7	10-18
		(*e*) Describe any sensitivity analyses	7	32-38
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5	21-36
		(b) Give reasons for non-participation at each stage	N.A.	N.A.
		(c) Consider use of a flow diagram	N.A.	N.A.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5	21-29
		(b) Indicate number of participants with missing data for each variable of interest	N.A.	N.A.
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	5	21-29
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*N.A.*	*N.A.*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	7; 8	33-38; 1-9
		Cross-sectional study—Report numbers of outcome events or summary measures	*N.A.*	*N.A.*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7	2-29
		(*b*) Report category boundaries when continuous variables were categorized	7; 8	33-38; 1-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8	1-9

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7	21-29
Discussion				
Key results	18	Summarise key results with reference to study objectives	9	2-30
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11; 12	35-38; 1-8
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9; 12	13-37; 1-8
Generalisability	21	Discuss the generalisability (external validity) of the study results	10; 11	10-38; 1-32
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12; 13	34-36; 1-3

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.