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REVIEW

Epidemiology of Mutations in the 65-kDa Retinal Pigment Epithelium (*RPE65*) Gene-Mediated Inherited Retinal Dystrophies: A Systematic Literature Review

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ABSTRACT

Introduction: Inherited retinal dystrophies (IRDs) represent a genetically diverse group of progressive, visually debilitating diseases. Adult and paediatric patients with vision loss due to IRD caused by biallelic mutations in the 65-kDa retinal pigment epithelium (*RPE65*) gene are often clinically diagnosed as retinitis pigmentosa (RP), and Leber congenital amaurosis (LCA). This study aimed to understand the epidemiological landscape of *RPE65* gene-mediated IRD through a systematic review of the literature, as the current evidence base for its epidemiology is very limited.

Methods: Medline, Embase, and other databases were searched for articles on the epidemiology of *RPE65* gene-mediated IRDs from inception until June 2021. Studies were included if they were original research articles reporting the epidemiology of RP and LCA and/or proportion of *RPE65* gene mutations in these clinically diagnosed or molecularly confirmed IRDs patients.

Results: A total of 100 studies with relevant data were included in this systematic review. The range for prevalence of LCA and RP in the literature was 1.20–2.37 and 11.09–26.43 per 100,000, respectively. The proportion of *RPE65* mutations in clinically diagnosed patients with LCA was found to be between ~ 2–16% within the US and major European countries (France, Germany, Italy, Spain, and the UK). This range was also comparable to our findings in the Asian region for *RPE65*-LCA (1.26–16.67%). Similarly, for these European countries, *RPE65*-RP was estimated between 0.23 and 1.94%, and *RPE65*-IRD range was 1.2–14%. Further, in the Americas region, mutations in *RPE65* were reported to cause 1–3% of RP and 0.8–3.7% of IRD cases. Lastly, the *RPE65*-IRD range was 4.81–8% in the Middle East region.

Conclusions: There are significant variations in reporting of *RPE65* proportions within

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countries as well as regions. Generating robust epidemiological evidence on *RPE65* gene-mediated IRDs would be fundamental to support rare disease awareness, timely therapeutic intervention, and public health decision-making.

Keywords: Epidemiology; Inherited retinal dystrophies (IRD); Leber congenital amaurosis (LCA); Prevalence; Retinitis pigmentosa (RP); *RPE65* gene; Systematic review

Key Summary Points

Robust epidemiology data for *RPE65*-mediated inherited retinal dystrophies (IRD) is limited and therefore accurate assessments of prevalence and incidence are challenging.

The prevalence of Leber congenital amaurosis (LCA) was estimated to be 1.20–2.37 per 100,000.

The proportion of *RPE65* mutations in clinically diagnosed cases of LCA:

European region: ranged between 1.79 and 22.22%. Americas region: ranged between 1.69 and 15.55%. The US and major European countries (France, Germany, Italy, Spain, and the UK): ranged between ~2 and 16%. Asian region: ranged between 1.26 and 16.67% (comparable to US and major European countries findings).

The prevalence of retinitis pigmentosa (RP) ranged between 11.09 and 26.43 per 100,000.

The proportion of *RPE65* gene mutation in clinically diagnosed cases with RP:

European region: ranged between 0.23 and 4.27%. Americas region: ranged between 0.81 and 3.28%. Major European countries (France, Germany, Italy, Spain, and the UK): ranged between 0.23 and 1.94%. The US: ranged between 0.81 and 1.85%.

INTRODUCTION

Inherited retinal dystrophies (IRDs) comprise a wide range of phenotypically and genetically heterogeneous group of rare genetic diseases that are generally characterised by progressive loss of vision [1, 2]. Mutations in more than 270 different genes have been identified as the cause of IRDs [3–5]. Among these, biallelic mutations in the *RPE65* gene, i.e., the gene that encodes the 65-KDa retinal pigment epithelium (RPE) mutations affect the visual cycle in the retinal epithelium, resulting in a progressive loss of photoreceptors. Rods and cones are two main types of photoreceptor cells. Rods are mainly found in the peripheral regions of the retina and are responsible for peripheral and night vision. Cone density is higher at the macular area and is responsible for colour vision and perception of fine details.

The gene *RPE65* retinoid isomerohydrolase is associated with three Online Mendelian Inheritance in Man (OMIM #180069) phenotypes, (1) autosomal recessive Retinitis pigmentosa 20 (RP), (2) autosomal recessive Leber's congenital amaurosis 2 (LCA), and (3) autosomal dominant Retinitis pigmentosa 87 with choroidal involvement [6]. While signs and symptoms are heterogeneous, RP is diagnosed in patients with gradual rod photoreceptor degeneration and good central vision within the first decade of life. RP is characterised by visual field (VF) loss and nyctalopia (poor night vision), and may progress to blindness [7]. In contrast, LCA is diagnosed in patients with rod-cone dystrophy who were either born blind or lost their low vision within the first year of life, and is characterised by a severe dystrophy of the retina [8–11]. LCA is mostly inherited as an autosomal recessive form, whereas RP can have any of the commonly recognized Mendelian inheritance patterns or maternal (mitochondrial) or digenic inheritance [6]. However, when RP is due to *RPE*65 biallelic variants, it has an autosomal recessive pattern of inheritance.

RP does not show any ethnic predilection; however, the most frequent pathogenic variants for RP-associated genes may vary for certain populations with a high rate of consanguinity

[12]. Further, it seems that there is no universally accepted diagnostic term for patients with retinal degeneration who lose vision during the first few years of life; various diagnostic terms were used in the literature with merely any genotypic differences, such as LCA type 2, early-onset severe retinal dystrophy (EOSRD), autosomal recessive childhood-onset severe retinal dystrophy (arCSR), autosomal recessive retinal dystrophy, severe early childhood-onset retinal dystrophy (SECORD), and/or early severe RP. EOSRD/SECORD is defined as a severe retinal dystrophy presenting after the first year of life and usually before the age of 5 years, whereas LCA is congenital or presents within the first few months of life, and both are characterised clinically by severe congenital/early infancy low vision, nystagmus, amaurotic pupils and markedly reduced/absent full-field electroretinograms [6, 13–15].

Although various terms are being used for clinical classification of the disease, the key for specifying a disease should be based on genetic testing, genotyping or molecular diagnosis [16]. It is also important to evaluate and classify the identified variants as pathogenic, non-pathogenic or likely pathogenic; or classify based on the American College of Medical Genetics and Genomics and the Association for Molecular Pathology guidelines for genetic variants [17, 18]. The pathogenicity classification of the variants and novel variants in the *RPE65* gene are described in some of the online databases for variants in human genetic mutations, which can support the molecular diagnosis of the disease, genetic counselling and medical management of the patient's condition [17, 19–21]. A natural history study highlighted the need for genetic testing, as it reported that there was limited information on phenotype correlations related to biallelic *RPE65* mutations, and that a number of clinical diagnostic terms were used for the same genotype with wider variation across all the different types of LCA [13].

The current evidence base for the epidemiology of *RPE65* gene-mediated IRDs is very limited. Such epidemiological evidence will be crucial for evaluating the impact of the disease in the population in terms of the burden of disease and identifying unmet clinical needs. Thus, this study aims to understand the epidemiology landscape of *RPE65* gene-mediated IRD, and to identify key knowledge gaps/unmet needs through a systematic review of the literature, focussing on mutations in the *RPE65* gene that are often clinically diagnosed as LCA and/or as RP [22, 23].

METHODS

Literature Search Strategy and Selection Criteria

A review of the medical literature was conducted as per the guidance of the Cochrane handbook for systematic reviews [24] and was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [25]. The electronic databases (Embase, Medline, Medline in-process and Cochrane Library) were searched from inception until the 25 June 2021 to retrieve studies reporting the prevalence and incidence of LCA and RP and the proportion of *RPE65* gene mutations in these IRDs patients. As *RPE65* gene-mediated IRDs are often clinically diagnosed as LCA or RP, the literature search was not designed to investigate other types of IRDs due to insufficient information in the publications. The Orphanet rare diseases platform [26, 27] and the bibliography of relevant literature reviews was also screened for including potential studies. Additionally, conference abstracts were hand-searched from the publication years of 2015 to June 2021 to retrieve the latest studies that have not yet been published in journals as full text articles or to supplement results of previously published studies. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

The databases were searched for terms related to *RPE65*, *RPE65*-IRD, *RPE65*-RP, *RPE65*-LCA, incidence, prevalence and/or epidemiology. The search results were limited to English language. The detailed literature search strategy for the various databases is presented in supplementary file 1. Studies related to *RPE65*

clinical trials, animal or in-vitro studies, case reports, review papers, studies describing pathogenicity/ molecular genetic features caused by *RPE65* mutations in a family or studies with mutations other than *RPE65*, etc. were excluded. Titles and abstracts of all the unique citations obtained were screened by two independent reviewers, and any discrepancies between the reviewers were reconciled by a third independent reviewer. The citations that did not match the eligibility criteria were excluded at the 'first pass', while unclear citations were included. Duplicates of citations (due to overlap in the coverage of the databases) were also excluded at the first pass stage. The full-text copies of all references that could potentially meet the eligibility criteria were downloaded.

Publications were included in the full-text review if they reported on prevalence/incidence of RP or LCA (irrespective of any mutation) or epidemiology of IRDs caused by *RPE65* gene mutations or proportion of *RPE65* gene mutation in RP or LCA. Additionally, some papers had presented results for LCA, EOSRD, severe early-onset retinal dystrophy (SEORD) and other similar terms separately, although there is no clear distinction between these diseases. In such cases, the data were included for patients identified with only LCA, RP, *RPE65*-IRD and/or related molecular diagnosis from populations to avoid discrepancies with such study methods. The percent proportions of the *RPE65* mutation within RP or LCA or IRD patients were calculated (if not explicitly mentioned in the paper) as the number of patients with *RPE65* mutations in a disease divided by the total number of patients with that disease.

The data from the included studies were extracted to data extraction grids by one reviewer, and checked by a second independent reviewer, with reconciliation of any differences by a third independent reviewer.

RESULTS

The literature search from the databases yielded 1066 citations from which 98 were removed as duplicates. Following the first pass of the citations, 118 potentially relevant references were identified for the second pass. Following detailed examination of these full-text articles, 65 were identified for inclusion after the second pass. Additionally, 35 were obtained by screening of bibliography citations and from hand-searching of relevant conference abstracts including two Orphanet site links [26, 27]. Thus, the final number of included citations for this review were 100 (Fig. 1).

While extracting the data from included papers, it was noted that some papers were reporting the study population for LCA, RP or IRD based on a diagnostic method, i.e., by either clinical and/or molecular/genetically confirmed diagnosis of the disease. This resulted in differences in the calculated proportions of *RPE65*-affected patients out of the study population. Thus, where applicable, we report both the clinical and/or the molecular data for a country in Tables 1 and 2 by individual patients as well as by families affected by the disease.

While reporting the percentage proportions, we tried to distinguish the populations with the relatively high prevalence of consanguineous marriages [28–31]. It was found that patients with high rate of consanguinity and those affected with recessive disease will be homozygous for their mutant allele [32].

Few papers only reported the proportion of *RPE65* gene mutation in patients with combined cohorts of RP and LCA patients (Supplementary Table A) and the proportion of *RPE65* gene mutation in an IRD cohort (Supplementary Table B).

Prevalence of LCA and the Proportion of *RPE65* Gene Mutation in LCA

The prevalence of LCA has been reported in three studies conducted in Denmark, Norway and the United States of America (US), and was estimated to be 1.20–2.37 per 100,000 [33–35].

The worldwide proportion of *RPE65* gene mutations in LCA families was estimated at 6.10% [36]. Within the clinically diagnosed cases of LCA, the proportions of *RPE65*-LCA across the global regions varied from 1.26% in China to 22.22% in the Netherlands [37, 38]. The proportion of *RPE65* mutations in LCA

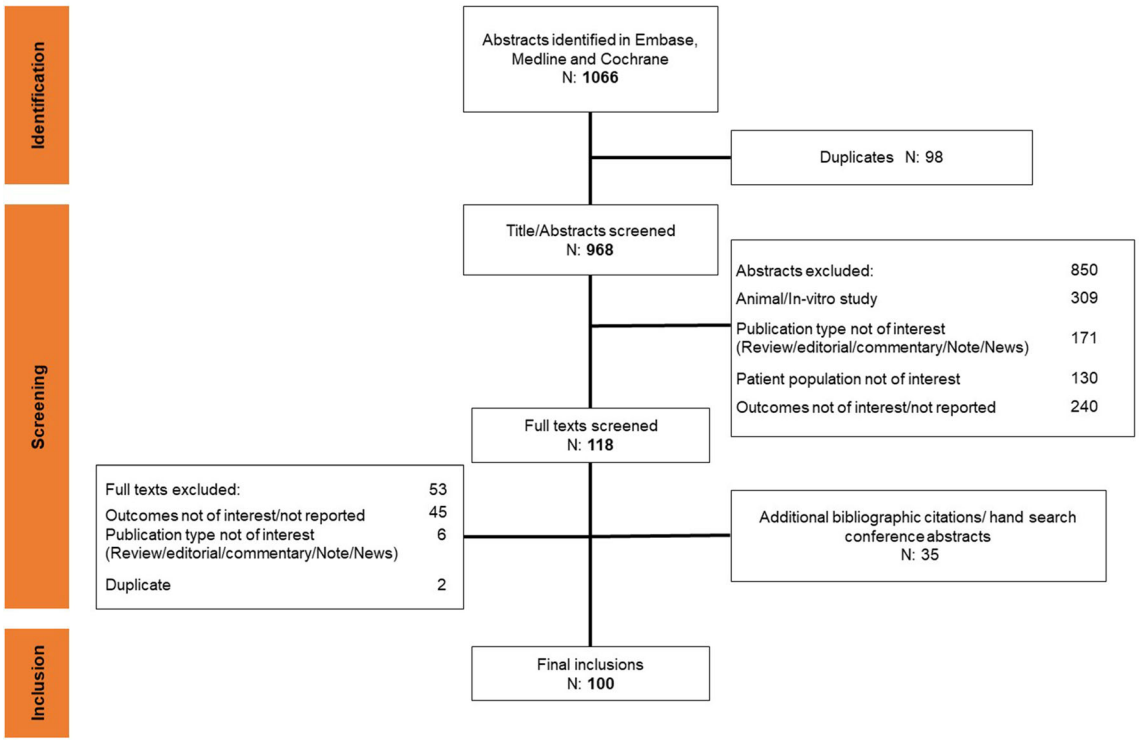

Fig. 1 PRISMA flow diagram of included and excluded publications

ranged between 1.79 and 16% in the five major European (EU-5) countries of France, Germany, Italy, Spain, and the United Kingdom (UK) [5, 39–44] and between 3.0 and 15.55% in the US [32, 45–49] (Fig. 2). A recent Costa Rican study [50] reported a very high prevalence of *RPE65*-LCA mutations at 95% which although an outlier from our defined ranges (1.26–22.22%) has nevertheless been included in Fig. 2. This phenomenon could be a genetic drift that may be due to a founder effect in the analysed samples from only the affected children and their immediate family members. Further, a Canadian hospital study reported 35.82% of *RPE65*-LCA mutations based on its sample analysing only the patients diagnosed with LCA [51]. The proportion of *RPE65* mutations in molecularly diagnosed LCA patients was based on a few studies varying from 3.95% in China to 20.51% in Brazil and up to 40% in Tunisia [37, 52–59] (Table 1).

Prevalence of RP and the Proportion of *RPE65* Gene Mutation in RP

Prevalence of RP was reported to range from 11.09 to 26.43 per 100,000 in the literature [34, 60–72] (excluding 47.62 per 100,000 for Israel's population due to high consanguinity [73]) (Fig. 3).

In the US, the prevalence of RP was 21.03 per 100,000 [65]; in the UK, it was between 20.54 and 25.03 per 100,000 [62, 66], while in the European region it ranged from 11.97 to 25.36 per 100,000 [61, 70]; for the Asian countries of China and Korea, it was the same as the global prevalence, i.e., 11.09–26.43 per 100,000 [60, 72]. For the Middle East country of Israel, it was high (47.62 per 100,000) [73].

It was also noted that populations with high rates of consanguinity and a high number of siblings per family report a much higher

Table 1 Proportion of *RPE65* gene mutations in molecularly diagnosed cases with LCA

Country	Proportion of *RPE65* mutations in LCA	Author, year of publication	Remarks
Ex-US and Ex-EU range for molecularly diagnosed patients was 3.95–20.51%			
China[a]	3.95[a]–15.0%[a]	Xu et al. [37] and Li et al. [52]	*RPE65* in 3/76 probands with LCA and the frequency of *RPE65* was at 15% in LCA/EOSRD/LCA + EOSRD patients
Oman[a]	7.41%[a]	Bruwer [53]	2 siblings out of 27 patients with LCA in consanguineous population genetically identified with disease-causing genes
Saudi Arabia	8.70%[a]	Khan et al. [54]	*RPE65* gene mutations identified in 2/23 consanguineous LCA children
India[a]	11.11%[a]	Viswarubhiny et al. [55]	*RPE65* gene mutations identified in 1/9 patients with LCA
Mexico[a]	13.33%[a]	Zenteno et al. [56]	*RPE65* gene variants were identified in 2/15 patients with LCA
Brazil[a]	19.08[a]–20.51%[a]	Motta et al. [57] and Sallum et al. [58]	*RPE65* gene mutations were identified in 16/78 and 29/152 patients with LCA
Tunisia[a]	40.0%[a]	El Matri et al. [59]	*RPE65* gene mutations were identified in 6/15 patients with LCA
Data as reported for molecularly diagnosed families			
Pakistan[a]	7.14%[a]	McKibbin et al. [127]	*RPE65* in 1/14 families diagnosed molecularly with LCA
UK[a]	12.18%[a]	Hull et al. [128]	*RPE65* gene mutations were identified in 24/197 EOSRD families genetically identified with disease-causing genes
Poland[a]	13.64%[a]	Skorczyk-Werner et al. [129]	*RPE65* gene variants were identified in 3/22 families diagnosed molecularly with LCA

EOSRD early-onset severe retinal dystrophy, *EU* European Union, *LCA* Leber congenital amaurosis
[a]The % proportion is based on molecularly diagnosed patients
Key messages from the table on the proportions of *RPE65* gene mutations in molecularly diagnosed LCA cases:
The proportions of *RPE65*-LCA mutations varied across the world. It was 3.95–15% in China; 8.7% in Saudi Arabia; 13.33% in Mexico; 20.51% in Brazil; and up to 40% in Tunisia
The frequency of *RPE65* mutations in a Chinese cohort of patients with LCA and EOSRD was 15% not only in the cohort total patients but also in LCA and/or EOSRD patient groups

Table 2 Proportion of *RPE65* gene mutation in RP

Country	Proportion of *RPE65* mutations in RP	Author, year of publication	Remarks
European countries range for clinically diagnosed was 0.23–4.27%			
Germany	0.23%	Weisschuh et al. [42]	One *RPE65* pathogenic variant in 434 patients with sporadic RP
Spain	1.02%	González-del Pozo et al. [74]	Potentially pathogenic 1 *RPE65* variant detected out of 98 ARRP patients
France	1.11%	Bocquet et al. [75]	*RPE65* was found in 1/90 ARRP individuals with consanguineous parents
Netherlands	1.55-4.27%	Haer-Wigman et al. [76] and Pierrache et al. [78]	*RPE65* was found in 2/129 and 44/1031 individuals with RP
Italy	1.94%	Colombo et al. [77]	*RPE65* variant in 2/103 patients with ARRP
Ireland	7.41%	Whelan et al. [5]	7.41% *RPE65* mutation was in patients with **dominant** RP
United States range for clinically diagnosed was 0.81–1.85%			
US	0.81–1.85%	Wang et al. [79] and Morimura et al. [49]	*RPE65* in 1/123 and 3/162 cases with RP Morimura 1998: study is of 147 individuals with ARRP and 15 with isolate RP
Mexico	2.7–10.34%	Zenteno et al. [56]	*RPE65* reported, in cases with 1/37 ARRP and 3/29 Simplex RP
Mexico	3.28%	Zenteno et al. [56]	Assumption calculation: *RPE65* in 4/122 RP patients
Range for molecularly diagnosed patients was 3–9.98% in EU and Americas			
Spain[a]	3.00%*	Perea-Romero et al. [80]	*RPE65* was at 3% in the genetically solved 666 ARRP cases
US[a]	3.23%*	Wang et al. [79]	*RPE65* in 1/31 cases genetically identified with disease-causing genes
Mexico[a]	3.45*–21.43%*	Zenteno et al. [56]	*RPE65* in cases with 1/29 ARRP and 3/14 Simplex RP
Mexico[a]	5.00%*	Zenteno et al. [56]	Assumption calculation: *RPE65* in 4/80 RP patients
Netherlands[a]	9.98%*	Pierrache et al. [78]	*RPE65* was found in 44/441 RP patients with a definite molecular diagnosis

Data as reported for clinically diagnosed families

Table 2 continued

Country	Proportion of *RPE65* mutations in RP	Author, year of publication	Remarks
Israel	0.43%	Kimchi et al. [124]	*RPE*65 mutation in 1/230 Ashkenazi Jewish descent clinically diagnosed families with RP
			While *RPE*65-RP was 1.16% (1/86) within the families genetically identified with disease-causing genes
India	2.94%	Singh et al. [125]	*RPE*65 variants in 1/34 clinically diagnosed ARRP consanguineous families
China	3.95%	Dan et al. [126]	*RPE*65 variants in 3/76 clinically diagnosed RP families
			While *RPE*65-RP was 7% (3/43) within the families genetically identified with disease-causing genes

ARRP autosomal recessive retinitis pigmentosa, *EU* European Union, *RP* retinitis pigmentosa

[a]The % proportion is based on molecularly diagnosed patients

Key messages from table on proportions of *RPE65* gene mutations in clinically diagnosed RP cases:

- The proportions of *RPE65*-RP in the EU-5 counties ranged between 0.23% in Germany and 1.94% in Italy
- The proportions of *RPE65*-RP across the European region ranged between 0.23% in Germany to 4.27% in the Netherlands (excluding Ireland's rare *RPE65* cases in patients with dominant RP)
- The proportions of *RPE65*-RP in the Americas region ranged between ~ 1% in the US and 3.28% in the Mexico (excluding Mexico's calculation for subgroup population with simplex RP)

Key messages from table on proportions of *RPE65* gene mutations in molecularly diagnosed RP cases:

- The proportions of *RPE65*-RP across the European and Americas region ranged between 3% in the US and Spain to 9.98% in the Netherlands (excluding Mexico's calculation for subgroup population with simplex RP)

prevalence. One such example was the study in Israel in which, due to high rates of consanguinity and a high number of siblings per family in some of the ethnic groups, a much higher prevalence of 1 in 2100 was found for non-syndromic RP (both in the Jewish and the Arab Muslim populations) in the Jerusalem area [73]. The prevalence was also found to be highest in the age group of 65 years and older [68, 69].

The proportion of the *RPE65* mutation in clinically diagnosed RP patients was reported to be between 0.23% (Germany) and 4.27% (the Netherlands) for the European region [42, 74–78]. For the EU-5, the proportion ranged from 0.23–1.94% [42, 77], while in the US, it was between 0.81 and 1.85% [49, 79] (Table 2). A Mexican study reported that *RPE65* in RP occurred in 3.28% of clinically diagnosed and 5% of the molecularly diagnosed probands [56]. The study by Wang et al. in the US [79] reported the proportion of *RPE65* mutation in molecularly diagnosed RP patients as 3.23% (vs. 0.81% in clinically diagnosed RP patients). The proportion of *RPE*65 mutation in molecularly diagnosed RP patients across the European and Americas region was between 3% in the US and Spain to 9.98% in the Netherlands [56, 78–80] (Table 2).

Proportion of *RPE65*-Mediated RP and LCA Combined

The following studies reported the proportion of the *RPE65* mutation out of the combined population of RP and LCA patients

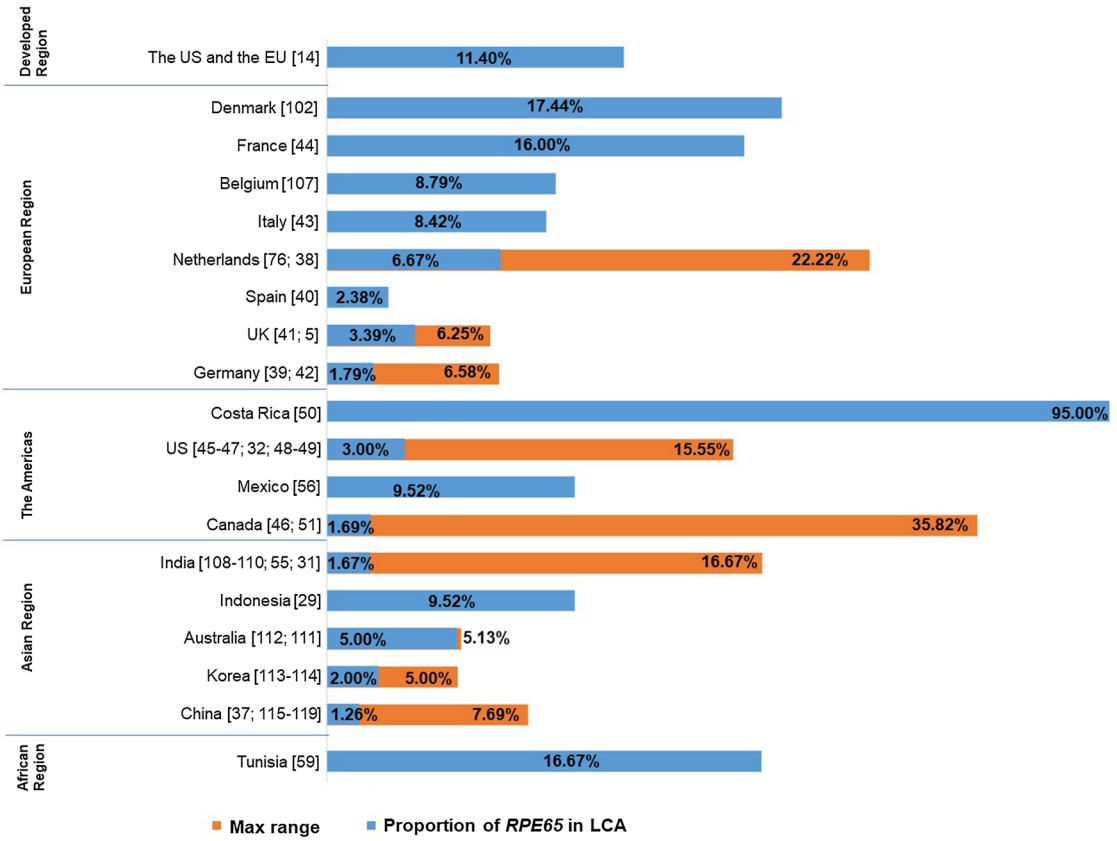

Fig. 2 Proportion of *RPE65* gene mutation in clinically diagnosed LCA patients. Source: Whelan et al. [5], Thompson et al. [14], Sitorus et al. [29], Verma et al. [31], Lotery et al. [32], Xu et al. [37], Booij et al. [38], Eisenberger et al. [39], Vallespin et al. [40], Henderson et al. [41], Weisschuh et al. [42], Simonelli et al. [43], Bocquet et al. [44], Dharmaraj et al. [45], Zernant et al. [46], Galvin et al. [47], Simovich et al. [48], Morimura et al. [49], Glen et al. [50], Heon et al. [51], Viswarubhiny et al. [55], Zenteno et al. [56], El Matri et al. [59], Haer-Wigman et al. [76], Astuti et al. [102], Coppieters et al. [107], Mamatha et al. [108], Sundaresan et al. [109], Srikrupa et al. [110], Thompson et al. [111], Lamey et al. [112], Surl et al. [113], Seong et al. [114], Liu, Bu [115], Li et al. [116], Chen et al. [117], Zhong et al. [118], Xu et al. [119]. The high *RPE65*-LCA 16.67% in South India [31] is based on 27/30 probands born through consanguineous marriage. The high *RPE65*-LCA 35.82% in Canada [51] is probably related to the paper's methodology to analyse only LCA patients with clinically and molecularly confirmed diagnosis identified at one of the hospitals with an ethnically diverse population. The very high prevalence of *RPE65* mutations (95%) in Costa Rica [50] is due to four founder mutations in *RPE65* which have been maintained in this genetically isolated population. The paper's methodology was to analyse samples from affected children and their immediate family members only. Additional data by families (not shown in Fig. 2): The Chinese paper [120] had reported *RPE65* mutations in 1% (1/100) families with LCA. The Chinese paper [82] had reported biallelic *RPE65* mutations in 2.97% (8/269) families with LCA. The Saudi Arabia paper [121] had reported *RPE65* mutations in 5.41% (2/37) consanguineous families with LCA. The Spanish paper [122] had reported *RPE65* mutations in 16.51% (18/109) families with LCA. The Indian paper [123] had reported *RPE65* mutations in 18.18% (2/11) families with LCA. Worldwide paper [36] had reported *RPE65* mutations in 6.15% (11/179) families with LCA. Key messages from Fig. 2 on proportions of *RPE65* gene mutations in clinically diagnosed cases of LCA: The proportions of *RPE65*-LCA across the world ranged between 1.26% in China to 22.22% in the Netherlands (excluding outliers from Costa Rica and Canada). The proportions of *RPE65*-LCA in the EU-5 counties ranged between 1.79% in Germany to 16% in France. The proportions of *RPE65*-LCA across the European region ranged between 1.79% in Germany to 22.22% in the Netherlands. The proportions of *RPE65*-LCA in the Americas region ranged between 1.69% in Canada to 15.55% in the US (excluding outliers from Costa Rica and Canada). The proportions of *RPE65*-LCA in the Asian region ranged between 1.26% in China to 16.67% in India. The proportion of *RPE65*-LCA across the US and Europe was at 11.4%

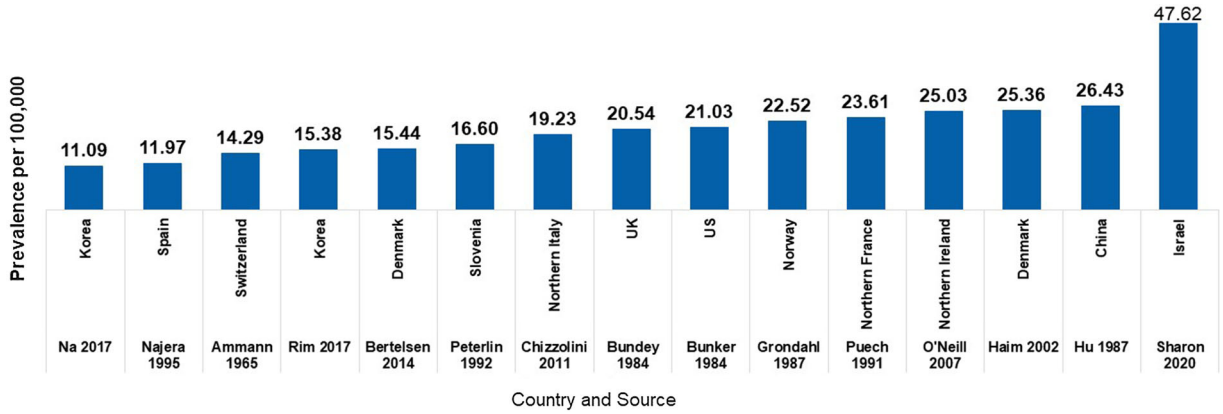

Fig. 3 Country-wise RP prevalence. Source: Bertelsen et al. [34], Hu [60], Haim [61], O'Neill et al. [62], Puech et al. [63], Grondahl [64], Bunker et al. [65], Bundey, Crews [66], Chizzolini et al. [67], Peterlin et al. [68], Rim et al. [69], Ammann et al. [70], Najera et al. [71], Na et al. [72], Sharon et al. [73]. The high prevalence (47.62) of RP in Israel [73] is based on consanguineous populations

(Supplementary Table A). In a Norwegian study with 513 isolated RP and LCA patients, 0.6% of the cases of *RPE65* mutation were observed [35]. A German study reported that the proportion of the *RPE65* mutation was 0.79% for the 126 patients with RP and LCA [39]. In a Dutch study, it was reported that the proportion of the *RPE65* mutation was 6% for the 35 patients diagnosed with juvenile autosomal recessive RP ($n = 17$), juvenile isolated RP ($n = 9$) and LCA ($n = 9$) [38]. Further, a study in Mexico reported that the proportion of the *RPE65* mutation was 4.20% for the 143 clinically diagnosed patients with RP and LCA. This proportion increased to 6.32% for the molecularly diagnosed 95 patients with RP and LCA [56].

Proportion of *RPE65* Gene Mutation in IRD

Few studies have reported the proportions of *RPE65* gene mutations in clinically diagnosed cases with IRD, varying from ~ 1% in China, US, UK and Israel to 14% in Germany [73, 76, 81–91], including the proportion of 8% in Iran and Tunisia's high-consanguineous population [89, 90]. One study reported the proportion of *RPE65*-IRD across the US and Europe as 2.06% [14]. The proportions of *RPE65*-IRD in the EU-5 counties and the European region ranged between 1.2% in the UK and 14% in Germany [83, 91]. Lastly, *RPE65* mutations were estimated at ~ 1% in the US, while for the Middle East region, it varied between 4.81% in Saudi Arabia and 8% in Iran's clinically diagnosed cases with IRD [81, 85, 87, 89]. Also, based on the available data, the proportions of *RPE65* in molecularly diagnosed cases with IRD was reported at 1.78% in China, 2.82% in the United Arab Emirates (UAE) and 4% in Brazil [57, 84, 92] (Supplementary Table B).

Another study analysed and predicted worldwide genetic prevalence of autosomal recessive IRD for biallelic *RPE65* gene in a total of 15,620 biallelic *RPE65* patients. This study expected that over 60% (9484 individuals) of these affected individuals would be from the African population, while only 9% would be Europeans [93].

Incidence of IRDs, RP and LCA

The genetic incidence of *RPE65*-IRD was 680 per 100,000 for the US population in a genetic testing study with 5879 cases submitted to the 'My Retina Tracker Genetic Testing Program' [94].

A population-based study conducted in Maine, US, between 1976 and 1980 evaluated

the incidence of RP. The study used medical and social service sources as the data source and estimated the birth incidence of persons who will become affected with non-syndromic RP as 28 per 100,000. The incidence of newly diagnosed RP cases per year was estimated to be 0.6 per 100,000 [65]. An epidemiological study of RP in Denmark reported that the average incidence between 1990 and 1997 was 0.79 persons per 100,000 population per year [61]. A nationwide population-based study from South Korea reported the incidence of RP over 4 years. This study found the average incidence of RP to be 1.64 cases per 100,000 person-years and that it was similar in men and women [69]. Further, a national registry study spanning over 15 years in Kuwait reported that RP was the leading cause for registered legal blindness driven by a high prevalence of consanguineous marriages. This study also observed fluctuations in RP incidence rates by age groups due to delay in visual impairment certification of many patients years after the onset of their disability or diagnosis [28].

The incidence of LCA was computed to be between 1 in 50,000 and 1 in 100,000 persons (i.e., approximately 1/75,000) in a multi-centre study analysing LCA patient cohorts from Europe and the US [46]. Additionally, LCA incidence also seems to be high in the consanguineous population of South India [29–31].

DISCUSSION

The clinical diagnosis of most *RPE65* patients is based on signs/symptoms, ophthalmologic features, and age of onset, while the molecular diagnosis of patients with *RPE65*-mediated IRD is based on pathogenic classification of variants identified on genetic tests with the use of various methods like next-generation sequencing, Sanger sequencing, whole exome-analysis or arrayed primer extension. Molecular diagnosis is important for the ophthalmologist to be able to analyse if the affected patient's condition can benefit from potential therapeutic interventions, like the new gene therapy treatments or IRDs clinical trials. Early diagnosis is important to deliver the potential gene therapy treatment to improve and preserve the visual function and therefore diminish the disease burden in affected patients [95]. Findings from the literature indicate that several disorders due to biallelic mutations in *RPE65* are named differently, and that the clinical aspects are overlapping, poorly defined and unreliable. They are all a clinical spectrum of the same disease generated by the *RPE65* enzymatic dysfunction, such as the phenotype of LCA 2 which is a little more severe and therefore clinically evident in a young population versus RP [13, 96–101]. Further, *RPE65*-mediated IRD may have different names based on the physician's assessment but have a similar set of symptoms. Therefore, the epidemiology of *RPE65*-mediated IRD should include all these diagnoses. However, in the literature, there are limited data for the epidemiology of *RPE65*-mediated IRDs as a group of diseases and instead the data for individual aetiologies were reported. Based on our review results, LCA and RP are ultra-rare IRDs with a prevalence ranging from 1.20 to 2.37 per 100,000 and from 11.09 to 26.43 per 100,000 persons, respectively. Also, the incidence of newly diagnosed RP cases per year was estimated to be about 0.6–1.64 per 100,000 population [61, 65, 69].

Epidemiological studies based on *RPE65* mutations in molecularly confirmed RP or LCA or IRD were also found to be scarce in the literature. Although the data on prevalence and incidence of *RPE65*-mediated IRD was limited, they indicated significant variation between countries and regions. Based on the clinical diagnosis of the disease in the UK, Ireland, Western Europe (France, Germany, Switzerland, Netherlands and Belgium), and Southern European countries (Italy and Spain), the frequency for *RPE65*-LCA cases was between 1.79 and 22.2%, *RPE65*-RP was 0.23–4.27%, and *RPE65*-IRD was around 1.2–14% [38, 39, 42, 76, 78, 83, 91]. *RPE65* variants have been reported to be most prevalent cause of LCA in the Nordic country of Denmark (17.44%) [102]. In North America, mutations in *RPE65* were reported to cause 3.0–15.55% of clinically diagnosed LCA cases in the US, 0.81–1.85% of RP in the US, 3.28% for *RPE65*-RP in Mexico and ~ 1% for

clinically diagnosed IRD cases in the US [45, 49, 56, 79, 81, 85]. In South America, the proportion were high due to the identification in the molecularly diagnosed Brazilian patients with only *RPE65*-LCA at 20.51% and *RPE65*-IRD at 4% [57, 58]. This could be because there were negative and inconclusive cases or could be attributable to the likelihood of the physician asking only suspected patients for a genetic test. This bias on asking for genetic tests would be much higher if the physician thinks that it could be a treatable IRD. For the Middle East region (Israel, Saudi Arabia and Iran), the proportion for *RPE65* mutations in IRD ranged between 1 and 8% [73, 87, 89]. In the African region (Tunisia), the frequency for *RPE65*-LCA was 16.67% [59]. Lastly, for the Asian region (Australia, China, India, Indonesia and Korea), the *RPE65*-LCA was 1.26–16.67% [31, 37] and the frequency for *RPE65*-IRD in China was 0.84–1.32% [82, 84].

While interpreting the results from this review, it is important to acknowledge several limitations. The main ones are related to factors like study design, population demographics (age, consanguineous marriages), enrolment criteria for patients, diagnostic criteria (clinical or molecular/genetic testing), ascertainment bias, classification, biological assaying techniques, etc., which made it difficult to compare the data between studies. It was also found that terms like probands, families, or individuals were used interchangeably in some of the studies, for which we had to rely on the term which was first described in the methods section or was mentioned on the figure/table from where the data were extracted. The literature search was mainly focussed on papers reporting *RPE65* in RP and/or LCA, so some other phenotypes with *RPE65* may have been missed due to a change in nomenclature. There might be intrinsic bias in the studies while distinguishing *RPE65* in RP or LCA due to a lack of clarity on the age of onset. The evaluation for the quality of included studies was not relevant as these were mainly genotyping studies and do not fit into conventional study types defined in the the quality assessment scale [103]. Further, the applicability of quality assessment checklist was limited as this literature review's scope was limited to the collation of epidemiological data without any quantitative meta-analysis.

CONCLUSIONS

Patients with *RPE65* gene-mediated IRD are reported from across the world, including in Europe, North America, South America, Middle East, and Asian countries. The proportion of *RPE65* gene mutation in IRD cohorts was around 1% in the countries of UK, Netherlands, US, Israel and China. It was noted that the range of ~ 2– ~ 16% for the proportions of *RPE65* mutations in patients with LCA was comparable between the EU-5 countries, the US and the Asian countries. Also, the proportions of *RPE65* mutations in patients with autosomal recessive RP was found to be between 1.02 and 2.7%. These ranges for *RPE65* in LCA and ARRP are comparable to previously reported reviews [104, 105].

Robust epidemiological data for *RPE65*-mediated IRDs are limited, and therefore accurate assessments of prevalence and incidence are challenging. Insufficient data on prevalence have contributed to the insufficient funding and resources available to conduct genetic testing for IRDs, and to provide genetic counselling for IRD patients and families [106].

There was a high heterogeneity in the reporting of the data, while the lack of sufficient high-quality studies highlights the need to conduct better quality studies on rare genetic diseases. We found that there were variations within the countries as well as between the regions in the reporting of the proportions of *RPE65* gene mutations, resulting in broad ranges for estimating the affected patient populations. Consanguineous populations were found to have outliers, as inheritance strongly influences the rate of prevalence in such rare genetic disorders. Therefore, due to limited evidence, further research is needed to generate robust evidence for better understanding of the epidemiology of *RPE65*-mediated IRDs and to diagnose the disease at an early stage. This would determine if the potential therapeutic intervention can provide the best chance to prevent progression to severe visual impairment

or complete blindness in affected patients. With the improvement in patient access and the quality of genetic tests, there is a possibility that, in coming years, ophthalmologists will be able to diagnose more cases with *RPE65*-mediated IRDs.

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