Prevalence of RPGR-mutated X-linked retinitis pigmentosa among males

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ABSTRACT

Background: X-linked retinitis pigmentosa (XLRP) is a rare inherited retinal disease predominantly affecting males.

Materials and methods: A comprehensive literature review was conducted to determine the prevalence of retinitis pigmentosa GTPase regulator (RPGR)-mutated XLRP. Identified studies were used to estimate four components among males: the prevalence of retinitis pigmentosa (RP), the proportion of RP that was X-linked, the proportion of misclassified inheritance type among RP cases, and the proportion of XLRP that was RPGR-mutated. Studies providing a direct estimate of XLRP prevalence were also included. The components’ sample size-weighted averages were combined to determine an overall prevalence estimate.

Results: The prevalence of XLRP was estimated to be between 2.7–3.5 per 100,000 males in the US, Europe, and Australia. After correction for misclassification, the prevalence increased to 4.0–5.2 per 100,000 males. Finally, the proportion of XLRP cases due to RPGR mutations was applied, resulting in an RPGR-mutated XLRP estimate of 3.4–4.4 per 100,000 males. Studies from other countries were consistent with the results for the overall XLRP prevalence but were not included in the final calculation because of regional variations and lack of detailed information.

Conclusions: These findings address an important gap in the understanding of RPGR-mutated XLRP by summarizing the global burden of this condition.

Introduction

Retinitis pigmentosa (RP) is a rare inherited retinal disease, broadly characterized by premature degeneration of rod and cone photoreceptors leading to early vision loss (1,2). RP can be inherited in an autosomal dominant, autosomal recessive, or X-linked pattern (3). X-linked RP (XLRP) is associated with a severe phenotype and early onset (4). Because of its X-linked inheritance pattern, the characteristic features of this condition are predominantly expressed by affected males (5). XLRP initially presents as night blindness in childhood and early adolescence, and in later stages it leads to profound central vision loss and legal blindness (5). Mutations in the retinitis pigmentosa GTPase regulator (RPGR) gene account for a majority of XLRP cases (5). To this end, genetic therapies specifically targeting RPGR are under investigation, although no therapies have been approved to date.

Understanding the global prevalence of RPGR-mutated XLRP is key in supporting changes in the treatment landscape and aiding the understanding of the impact of the potentially treatable patient population on the healthcare system. To date, no published studies have estimated the prevalence of RPGR-mutated XLRP; prior studies have only provided components of the overall prevalence (e.g., proportion of RP that is X-linked). The goal of this review was to synthesize available literature and use the components of the overall prevalence to estimate the prevalence of RPGR-mutated XLRP among males.

Methods

Search strategy and selection criteria

A comprehensive search of literature published through March 2021 was conducted using a combination of relevant subject headings and text words to represent Retinitis Pigmentosa and each of the areas under investigation (e.g., X-linked inheritance among males with RP, RPGR mutation among persons with XLRP). Records were limited to English language and humans. The most relevant references were used to identify additional studies through PubMed Similar Article and Web of Science Cited References. The complete search strategy is outlined in Supplemental Material (Appendix 1). Relevant references from reviewed studies were also assessed for potential inclusion. An Ethical Statement is not applicable as the conduct of this literature review did not involve any human or animal subject.

Study outcomes

Regions identified through the literature review included the United States, Europe, Australia, Middle East, India, and East Asia, which were further grouped into three combined regions (United States/Europe/Australia, Middle East/India, and East Asia) based on location, development, and reported consanguinity. The median estimates and weighted averages (based...
on the study population size) were summarized for each region. Studies on the prevalence of XLRP were classified as direct estimates (studies that reported the prevalence of XLRP) and indirect estimates (studies that reported the prevalence of RP or the proportion of RP cases that were X-linked, which were combined to estimate the prevalence of XLRP).

Studies have reported a significant proportion of clinically classified autosomal dominant and simplex cases were later found to have X-linked inheritance (7–10). The reverse pattern of misclassification (i.e., another inheritance type misclassified as XLRP) did not occur with appreciable frequency. Therefore, an adjustment for misclassification of XLRP was applied to the estimated prevalence. Adjustment for misclassification was based on the proportion of RP cases with inheritance types other than X-linked that were reclassified after genotyping (with requirement that studies clearly state that the open reading frame 15 (ORF15) region was screened), as well as the prevalence of those inheritance types.

Specifically, the weighted average for identified studies that measured the proportion of autosomal dominant cases reclassified as XLRP after genotyping was calculated. Additionally, the weighted average for the proportion of all RP cases clinically categorized as autosomal dominant was estimated. These averages were multiplied together to determine the proportion of all RP cases that were XLRP but clinically categorized as autosomal dominant. The same steps were completed for simplex cases. The XLRP misclassification factor was then determined by adding the proportion of reclassified XLRP cases to the uncorrected proportion of RP cases that are XLRP and then dividing by that same uncorrected proportion.

The proportion of XLRP due to RPGR mutations was estimated using studies that clearly stated that ORF15 mutations were screened in the study population. The proportion of RPGR mutations resulting in XLRP was estimated and noted whether the proportion was among individuals or families.

Results

Estimating the prevalence of XLRP

United States/Europe/Australia

Direct method. Two studies assessed the prevalence of XLRP directly in the population, one from Denmark and one from the United States (Table 1) (11,12). Of note, a second study has been published from Denmark but uses the same population and has similar results (15). In order to avoid double counting the same population, only the most recent study was included. The estimates of prevalence from the included studies in the United States and Denmark were similar: 2.3 and 3.8 per 100,000 males, respectively, with a median of 3.1 per 100,000 males. The weighted average of these studies provided a prevalence estimate of 3.5 per 100,000 males.

Indirect method. Seven studies reported a range of 12.2 to 28.0 and a median of 21.5 per 100,000 males for the prevalence of nonsyndromic RP among males in the United States and Europe (Table 1) (11,13–18). The weighted average for the prevalence was 19.6 per 100,000 males.

Eight studies reported a range of 4.0% to 21.2% and a median of 10.8% for the proportion of RP cases classified as X-linked among males in the United States, Europe, and Australia (Table 1) (11,15,17,19–23). The weighted average estimate of XLRP among males was 13.7%. Six studies used data from affected male individuals and two studies used data from families (11,15,17,19–23). The median percentage of males with XLRP counted in individuals (12.6%) and family units (9.6%) were comparable; thus, both types of studies were included in the estimation of XLRP.

Utilizing the estimates derived from the literature on the prevalence of RP and the proportion of RP that was due to X-linked inheritance, the overall prevalence of XLRP was indirectly estimated. Using the medians for the prevalence of RP among males (21.5 per 100,000; Table 1) and the proportion of RP that was XLRP (10.8%; Table 1), the prevalence of XLRP was estimated to be 2.3 per 100,000 males. Similarly, using the weighted averages for the prevalence of RP among males (19.6 per 100,000; Table 1) and the proportion of RP that was XLRP (13.7%; Table 1), the prevalence of XLRP was estimated to be 2.7 per 100,000 males.

Middle East/India

No studies directly estimating the prevalence of XLRP were retrieved from the Middle East or India; as such, only an indirect method of estimation was possible. For this region, few studies have been published on RP prevalence among males (Table 2) (24–26). One study from Israel examined the prevalence of RP in the Jerusalem region (26). Two studies from India used population-representative door-to-door surveys to yield prevalence estimates of RP (24,25). However, one study was limited to people aged 40 and older and the other study did not provide a breakdown of cases by sex. Despite these factors, which limit the precision of estimations of male RP prevalence, considerable evidence demonstrated that male RP prevalence (and RP prevalence generally) was higher in the Indian and Israeli populations studied than in the United States/Europe/Australia populations studied. Whereas the median RP prevalence in the United States/Europe/Australia studies was 21.5 per 100,000 males, as shown in Table 1, the prevalence of male RP was estimated to be 54.60 per 100,000 males in the Israeli study and 71.03 and 90.84 per 100,000 males in the Indian studies (Table 2).

Few studies reported the proportion of XLRP among families with RP in Israel and India (Table 2) (26–28). In most cases, compared with the United States/Europe, these studies reported a smaller proportion of cases that were XLRP, ranging from 2.8% to 6.6%. The median was 3.9% and the weighted average was 5.2%. When applying the median proportion of XLRP from Table 2 (3.9%) to the median RP prevalence estimate from Table 2 (71.03 per 100,000 males), the prevalence of RP was ~2.8 per 100,000 males, similar to the prevalence observed in the United States and Europe. Utilizing the weighted average for the proportion of XLRP also provided a similar result of 2.8 per 100,000 males.
Table 1. Summary of studies on the prevalence of XLRP, the prevalence of RP, and the proportion of RP with X-linked inheritance among males in the United States, Europe, and Australia.

| Study                      | Location              | Number of cases | Total male population\(^a\) | Prevalence per 100,000 males |
|---------------------------|-----------------------|-----------------|-----------------------------|-------------------------------|
| Studies directly estimating the prevalence of XLRP |                       |                 |                             |                               |
| Bunker et al. 1984 (11)   | United States (Maine) | 13              | 562,330                      | 2.32                          |
| Prokisch et al. 2007 (12) | Denmark               | 96              | 2,519,458                    | 3.81                          |
| Studies estimating the prevalence of RP |                       |                 |                             |                               |
| Boughn et al. 1980 (13)   | United States         | 347             | 1,239,285.7                  | 28.00                         |
| Bundey and Crews 1984 (14)| United Kingdom (Birmingham) | 112         | 520,500                      | 21.52                         |
| Bunker et al. 1984\(^b\) (11) | United States (Maine) | 127.64         | 562,330                      | 22.70                         |
| Haim 2002\(^2\) (15)      | Denmark               | 581.25          | 2,564,627                    | 22.66                         |
| Holtan et al. 2020\(^3\) (16) | Norway (southeast region) | 181.14    | 1,488,861.5                  | 12.17                         |
| Nájera et al. 1995 (17)   | Spain (Valencia)      | 149             | 1,098,945.5                  | 13.56                         |
| Peterlin et al. 1992 (18) | Slovenia              | 104             | 689,655.2                    | 15.08                         |

Table 2. Summary of studies on the prevalence of RP and the proportion of RP with X-linked inheritance among males in Israel and India.

| Study                      | Location              | Number of RP cases | Total male population | Nonsyndromic RP prevalence per 100,000 males |
|---------------------------|-----------------------|-------------------|-----------------------|----------------------------------------------|
| Studies estimating the prevalence of RP |                       |                   |                       |                                              |
| Nirmalan et al. 2006 (24) | India (central)       | 4.41\(^a\)        | 4,854                 | 90.84                                        |
| Sen et al. 2008 (25)      | India (southern)      | 2.37\(^b\)        | 3,334                 | 71.03                                        |
| Sharon and Banin 2015 (26)| Israel (Jerusalem)    | 258               | 472,500\(^c\)         | 54.60                                        |
| Studies estimating the proportion of RP with X-linked inheritance |                       |                   |                       |                                              |
| Kar et al. 1995 (27)      | India (Chennai)       | 2                 | 72                    | 2.8%                                         |
| Sharon and Banin 2015 (26)| Israel (Jerusalem)    | 12                | 183                   | 6.6%                                         |
| Vinchurkar et al. 1996 (28)| India (Pune)          | 3                 | 76                    | 3.9%                                         |

East Asia

No studies directly estimating the prevalence of XLRP were identified for East Asia. The only prevalence study for RP reported from Asia (exclusive of India, reported in the previous section) was conducted in South Korea (29). However, the methods for this study were different than those of other RP studies. This study utilized an insurance claims database, which resulted in a large denominator population but also could result in an underestimation of prevalence if RP cases were not coded as such in the database. The study identified an estimated 3,729 males with RP among 23,840,896 males according to the 2010 national census, resulting in a prevalence estimate of 15.64 per 100,000 males.

Two studies from East Asia reported on the proportion of XLRP among families with RP (30,31). A study from China included 224 RP families, of which 20 were classified as having XLRP (8.9%) (31). One study from Japan reported 3.4% of
males with RP had X-linked inheritance; however, less weight should be given to the findings of this study (30). First, the authors stated that their study included small family units, making determination of inheritance type difficult. Additionally, consanguinity was potentially a factor, and increased consanguinity will result in a higher proportion of autosomal recessive inheritance, thus forcing the proportion of other inheritance patterns lower (30). In studies of Israel/India, populations with high consanguinity had a lower proportion of XLRP but also a higher prevalence of RP, which resulted in a similar overall prevalence for XLRP. This may also be true in Japan, but not enough information is available to draw a firm conclusion.

**Misclassification of inheritance pattern in RP**

In all of the studies used to estimate the prevalence of XLRP in males, the classification of a subject as having an X-linked inheritance pattern was determined clinically, from pedigrees and ophthalmologic findings. In practice, the post-genotyping reclassifications involving XLRP that occurred with appreciable frequency were: (1) autosomal dominant (AD) to XLRP and (2) simplex/sporadic to XLRP. Studies addressing the frequencies of these types of misclassification are summarized in Table 3 (7,9,10,32). The prevalence of XLRP needed to be adjusted upwards to account for this underdiagnosis. The proportion of all RP cases that would be newly given an XLRP classification after genotyping was estimated using the weighted average of proportions listed in Table 3 and the prevalence of AD and simplex cases (information obtained from high-quality studies used to determine the proportion of XLRP among RP; studies are listed in Supplemental Tables S1 and S2) (7,9–11,15,17,19–22,32). Utilizing the misclassification from Table 3 and the proportion of AD and simplex cases from Supplemental Tables S1 and S2, it was determined that the prevalence of XLRP in the United States and Europe should be multiplied by a factor of 1.489 to correctly estimate the prevalence of XLRP. Utilizing the indirect estimate's weighted average calculated above, likely an additional ~1.3 cases per 100,000 males were clinically diagnosed as AD or simplex but were in actuality X-linked inheritance. This was similarly applied to the studies directly estimating the prevalence of XLRP, with the added assumption that the proportion of inheritance was similar in that region, resulting in an addition of 1.7 cases per 100,000 males. Of note, because of a lack of information from all regions, only studies from the United States and Europe were included here. An assumption needs to be made that misclassification will be the same in all countries. Thus, using the weighted averages of 2.7 to 3.5 as the range of potential clinically diagnosed XLRP prevalence estimates, the true prevalence of XLRP, including individuals who were misdiagnosed with a different inheritance pattern, was 4.0 to 5.2 per 100,000 males.

**Proportion of XLRP comprised of RPGR mutations**

Eighteen studies examined the proportion of XLRP cases with RPGR gene variants (Supplemental Table S3) (8,10,23,26,31,33–45). The studies reported a range of 58.3% to 100% with a median of 88.5% and a weighted average of 84.3% among individuals/families with XLRP and a known variant. When the studies with small sample size were removed (N ≤ 20), 11 studies remained and the reported range changed to 74.7% to 91.9% (Table 4), but the median and weighted average remained almost identical (88.5% and 84.4%, respectively) (8,10,23,34,35,37,39–42,44). The proportion is lower when including all screened cases (known and unknown variants) but, over time, the proportion of unknown variants is decreasing as more variants are continuously identified. For this study, only the proportion among individuals with known variants is utilized, which assumes that the distribution of RPGR among unknown variants will be the same as among the known variants.

**Final estimation of RPGR-mutated XLRP prevalence among males**

Overall, the prevalence of RPGR-mutated XLRP among males was similar across countries, although assumptions must be made about misclassification of inheritance, and limited information was available for some regions. Therefore, the final estimates were based on the United States/Europe/Australia where the most information was identified. The prevalence of XLRP was estimated to range from 4.0 to 5.2 per 100,000 males. When applying the proportion of XLRP cases due to RPGR mutations, the final prevalence was estimated to be 3.4 to 4.4 per 100,000 males (Figure 1).

| Study | Location | Able to detect mutations in ORF15 exon? | Original classification of RP inheritance pattern (number of individuals) | Number of individuals for which inheritance pattern was reclassified as XLRP after genotyping | % reclassified as XLRP |
|-------|----------|----------------------------------------|-------------------------------------------------|-----------------------------------------------|------------------------|
| Churchill et al. 2013 (9) | United States (primarily TX, CA, MI) | Yes | Autosomal dominant (258) | 22 | 8.5% |
| Birtel et al. 2018 (32) | Germany (Bonn) | Yes | Autosomal dominant (17) | 1 | 5.9% |
| Branhm et al. 2012 (7) | United States (primarily TX, CA, MI) | Yes | Simplex (185) | 28 | 15.1% |
| Birtel et al. 2018 (32) | Germany (Bonn) | Yes | Simplex (70) | 10 | 14.3% |
| Neidhardt et al. 2008 (10) | Switzerland | Yes | Simplex (39) | 0 | 0% |

ORF, open reading frame; RP, retinitis pigmentosa; XLRP, X-linked retinitis pigmentosa. *Based on pedigree and clinical observations. aChurchill 2013 and Branhm 2012 drew (non-overlapping) samples from the same cohort.
Table 4. Summary of studies on the proportion of RPGR mutations among individuals/families with XLRP.

| Study                  | Location                                      | Number with any XLRP mutation identified | % RPGR among those with any known mutation for XLRP | % among all genetically evaluated |
|------------------------|-----------------------------------------------|------------------------------------------|-----------------------------------------------------|----------------------------------|
| Bader et al. 2003 (34) | Germany (93%)†                               | Individuals 58                          | 37                                                  | 91.9%                            | 58.6%                           |
| Bocquet et al. 2013 (35)| France                                        | Families 26                              | 22                                                  | 20                               | 90.0%                           | 76.9%                           |
| Breuer et al. 2002 (8) | North America                                 | Individuals 185                         | 70                                                  | 60                               | 85.7%                           | 32.4%                           |
| Koyanagi et al. 2019 (37)| Japan                                        | Individuals N/A                         | 26                                                  | 23                               | 88.5%                           | N/A                             |
| Motta et al. 2018 (39) | Brazil                                        | Individuals N/A                         | 21                                                  | 19                               | 90.5%                           | N/A                             |
| Neidhardt et al. 2008 (10)| Germany, The Netherlands, Denmark, and Switzerland | Individuals 90†                         | 46                                                  | 37                               | 80.4%                           | 41.1%                           |
| Pelletier et al. 2007 (40) | France                                      | Individuals 88                          | 69                                                  | 55                               | 79.7%                           | 62.5%                           |
| Perea-Romero et al. 2021 (41) | Spain                                | Families N/A                           | 91                                                  | 68                               | 74.7%                           | N/A                             |
| Pontikos et al. 2020 (42)| United Kingdom                               | Individuals N/A                         | 275                                                  | 229                              | 83.3%                           | N/A                             |
| Sharon et al. 2003 (44) | Majority from United States and Canada       | Individuals 187                         | 90                                                  | 80                               | 88.9%                           | 42.8%                           |
| Weisschu et al. 2020 (23)| Germany (southwest)                        | Individuals 110                         | 103                                                  | 92                               | 89.3%                           | 83.6%                           |

N/A, not available; RPGR, retinitis pigmentosa GTPase regulator; XLRP, X-linked retinitis pigmentosa. †54 cases from Germany and one case from each of the following countries: Croatia, Luxembourg, Switzerland, and Spain. ‡Number unclear in the manuscript.

Discussion

This literature review has examined studies from multiple countries and applied the information retrieved for the specific components required to estimate the prevalence of RPGR-mutated XLRP among males. The overall prevalence of XLRP was determined to be 4.0 to 5.2 per 100,000 males and an estimated prevalence of RPGR-mutated XLRP cases was 3.4 to 4.4 per 100,000 males. To determine the prevalence of RPGR-mutated XLRP in the United States/Europe/Australia, estimates from direct reports, as well as indirect calculations by estimating the prevalence of RP and the proportion of RP that is XLRP, were used. Estimates generated utilizing the indirect method were similar to those from direct studies. The similarity in these estimates provided confidence in the prevalence estimates for this region.

The differences observed in RP prevalence by region are likely explained by the higher frequency of consanguineous marriage in some regions of Israel and India. The odds of having RP were higher among individuals with a consanguineous family history compared to people not reporting consanguinity (24,26). Thus, the prevalence of RP reported in studies from regions with a higher frequency of consanguineous marriages was higher. Similarly, consanguinity of the populations in these regions is possibly the

**Figure 1.** Graphical representation of the calculation of prevalence estimates for RPGR-mutated XLRP in the United States and Europe.
reason the proportions with X-linked inheritance were smaller than those observed in studies from the United States and Europe. Consanguinity will result in a higher number of autosomal recessive cases in the population but will not increase the number of X-linked inheritance cases. In other words, among the overall classification categories of RP, autosomal recessive will take a bigger share, which will lead to a smaller proportion of XLRP cases. In countries with a lower proportion of X-linked inheritance, the prevalence of RP was also larger, resulting in very similar estimates for the prevalence of XLRP in the United States/Europe compared to India/Israel.

Overall, very little information on the prevalence of XLRP among males was available for East Asia. Using the few studies available, the prevalence appeared to be lower than in the United States and Europe but that cannot be stated with certainty. Additionally, the similarity in XLRP prevalence across the United States, Europe, and Middle East/India regions supports the idea that the prevalence of this RP subtype may be similar across different geographic areas. Future studies from East Asia will allow for assessment of these assumptions and whether East Asia should have a separate determination of prevalence estimates.

Studies included in certain sections of this review were required to have clear methods regarding genotyping and the inclusion of the ORF15 region when genotyping. However, the type of genotyping is important to consider because mutations in ORF15 can be easily missed by common sequencing methods, underestimating the proportion of RPGR mutations (a large majority of RPGR mutations occur in this mutational hotspot) (46). This underscores the importance of genotyping technique when studying XLRP and illustrates why this review only utilized studies with genotyping that included the ORF15 region.

To date, only one population-based study has reported on the prevalence of XLRP among females, providing an estimate of 5.44 per 100,000 females (12). The authors noted that this may be an underestimate due to unascertained cases (e.g., asymptomatic cases without affected children). Among the females with XLRP, 19.8% were noted to be “affected” carriers. The designation of affected versus unaffected varied strongly by age, with younger females less likely to be classified as affected. Other studies of symptoms among women with XLRP have reported on a range of visual impairment measures (38,47–49). Symptoms ranged from none to blindness, but a commonality among the studies was that not all females were asymptomatic and some did experience severe visual impairment (38,47–49). For this review, determining an overall prevalence estimate for women was not undertaken because only one study reports a prevalence estimate; no studies evaluated misdiagnosis in a female population; non-detection of asymptomatic females is an issue; and the definition of symptomatic women varied greatly, resulting in difficulty in providing an assessment of overall prevalence versus prevalence of symptomatic women.

Although this review included numerous studies, limited information was available for certain regions. Few studies were available for East Asian countries. Additionally, few studies were available for the region of Israel and India. Although studies utilized for those regions demonstrated consistency and appear to be representative of consanguineous populations, further studies are needed to determine this with certainty. This assessment was also limited in that studies of misclassification of inheritance were only available for the United States and Europe. Again, assumptions were made that this misclassification would be similar across countries, but that needs to be proven by quantitative studies from these regions.

In summary, using a multistep approach to summarizing the literature, the prevalence of RPGR-mutated XLRP was estimated to be 3.4 to 4.4 per 100,000 males. This study is the first to combine multiple components of the literature to determine a specific estimate for RPGR-mutated XLRP prevalence. These findings address an important gap in the understanding of RPGR-mutated XLRP by providing additional clarity around the prevalence of this condition.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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