Frequency and Genetic Spectrum of Inherited Retinal Dystrophies in a Large Dutch Pediatric Cohort: The RD5000 Consortium

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Received: March 8, 2024
Accepted: August 3, 2024
Published: August 27, 2024

Citation: Heutinck PAT, van den Born LI, Vermeer M, et al. Frequency and genetic spectrum of inherited retinal dystrophies in a large dutch pediatric cohort: The RD5000 consortium. *Invest Ophthalmol Vis Sci.* 2024;65(10):40. https://doi.org/10.1167/iovs.65.10.40

Purpose. Gene-based therapies for inherited retinal dystrophies (IRDs) are upcoming. Treatment before substantial vision loss will optimize outcomes. It is crucial to identify common phenotypes and causative genes in children. This study investigated the frequency of these in pediatric IRD with the aim of highlighting relevant groups for future therapy.

Methods. Diagnostic, genetic, and demographic data, collected from medical charts of patients with IRD aged up to 20 years (n = 624, 63% male), registered in the Dutch RD5000 database, were analyzed to determine frequencies of phenotypes and genetic causes. Phenotypes were categorized as nonsyndromic (progressive and stationary IRD) and syndromic IRD. Genetic causes, mostly determined by whole-exome sequencing (WES), were examined. Additionally, we investigated the utility of periodic reanalysis of WES data in genetically unresolved cases.

Results. Median age at registration was 13 years (interquartile range, 9–16). Retinitis pigmentosa (RP; n = 123, 20%), Leber congenital amaurosis (LCA; n = 97, 16%), X-linked retinoschisis (n = 64, 10%), and achromatopsia (n = 63, 10%) were the most frequent phenotypes. The genetic cause was identified in 76% of the genetically examined patients (n = 473). The most frequently disease-causing genes were *RS1* (n = 32, 9%), *CEP290* (n = 28, 8%), *CNGB3* (n = 21, 6%), and *CRB1* (n = 17, 5%). Diagnostic yield after reanalysis of genetic data increased by 7%.

Conclusions. As in most countries, RP and LCA are the most prominent pediatric IRDs in the Netherlands, and variants in *RS1* and *CEP290* were the most prominent IRD genotypes. Our findings can guide therapy development to target the diseases and genes with the greatest needs in young patients.

Keywords: inherited retinal dystrophy, gene therapy, pediatric

Inherited retinal dystrophies (IRDs) are a clinically heterogeneous group of monogenic diseases causing retinal degeneration or dysfunction often resulting in severe vision loss. IRDs are the most important cause of juvenile blindness in the Western world.[1] Incidence rates vary from 1:4000 for retinitis pigmentosa (RP) to 1:40,000 for achromatopsia and 1:50,000 to 100,000 for choroideremia.[2–4] Not only the phenotypes and frequencies of IRD are highly variable, but the genetic causes are heterogeneous as well: mutations in more than 300 genes have been identified.[5]

Among the most fascinating breakthroughs in retinal research are the developments in gene-, pathway-, and cell-based therapies for IRD. Recent advances in molecular genetics have enabled a better understanding of the mechanisms of retinal dysfunction, which has boosted research. Currently, treatment strategies for multiple IRD genes are at various stages of development.[5–8] The first approved gene therapy for *RPE65*-related IRD was voretigene neparvovec (Luxturna, Spark Therapeutics, Inc, Philadelphia, PA, USA), which is now widely applied.[9–11]

Most gene therapy strategies are based on viral vectors, carrying an intact copy of the gene involved, infecting vital retinal and retinal pigment epithelial cells. In order to rescue visual function, a considerable proportion of these cells need to be intact at the time of treatment. The time frame during which treatment can be most effective, termed "the window of opportunity," varies by the type of IRD and causal gene.[12] For example, natural course studies for IRD caused by *RPE65* showed that vision often remains functional during the first decade of life, and visual decline usually initiates around the age of 15 to 20 years. After the age of 20, an acceleration of visual loss is observed in virtually everyone.[13] This implies that young patients with IRD will benefit most from the upcoming treatments. Hence, identification of these young patients is of high relevance.

Comprehensive clinical studies addressing the prevalence of IRD, the genetic causes, and the natural course of disease are needed to identify the window of opportunity for effective intervention prior to irreversible vision loss. Current reports primarily focus on the natural course and epidemiology of IRD in adults, with limited data on children.[14–16] In the Netherlands, the RD5000 database serves as a centralized, web-based registry of patients with IRD, facilitating uniform data management, research, and patient selection for potential therapies and clinical studies.[17] Our study utilized this database to identify Dutch children diagnosed with IRD, aiming to determine the frequencies of phenotypes and genetic causes of IRDs, with a focus on identifying key groups for advancing therapeutic interventions.

Methods

This descriptive study with retrospective analyses included all children and adolescents who had been registered in the national RD5000 database and received a diagnosis of IRD before the age of 20 years. The RD5000 database is a web-based database for IRD with ongoing data collection, focusing on standardized data registration, pseudo-anonymized storage, and controlled web-based data sharing among the Dutch tertiary eye care centers. The objective of the RD5000 database is to register all patients with IRD in the Netherlands. Each center can input data on their patients with IRD into the database, which may become accessible for research with the center's approval.[17] The RD5000 study protocol obtained ethical approval from the medical ethics committee (MEC-2010-359) of the Erasmus Medical Center. For our study, data on demographics, phenotypes, clinical data, and results from genetic examinations from all patients were actively collected from medical charts from 2017 until 2020 ($N = 624$ [100%]; males, $n = 395$ [63%]). Prior to the collection of clinical data, informed consent was obtained from the patient and/or their parents/guardians after providing them with relevant information.

IRD was defined as a monogenic disease causing retinal degeneration or dysfunction, characterized by functional loss of photoreceptors with characteristic multimodal imaging findings. All patients had visited the outpatient clinic at one of the following participating ophthalmogenetic centers of the RD5000 study (Amsterdam University Medical Center, University Medical Center Utrecht, University Medical Center Groningen, Leiden University Medical Center, Radboud University Medical Center, Erasmus Medical Center, the Rotterdam Eye Hospital, and Bartiméus). In the clinic, the diagnostic process for IRD comprises ophthalmic examination, electroretinography, multimodal retinal imaging, and optionally electrooculography and visual field testing. Furthermore, with the consent of parents and/or patients, genetic testing was often conducted as part of the diagnostic process. Derived from clinical charts and genetic testing outcomes, a primary phenotype of IRD was established.

Phenotypes were categorized as nonsyndromic IRD and syndromic IRD (IRD in combination with other organ disease). The nonsyndromic IRDs were further classified in progressive and stationary IRD.

Next-generation sequencing including whole-exome sequencing, data analysis and extensive gene package analysis, segregation analysis, and diagnostic Sanger sequencing were performed at one of the three ophthalmogenetic laboratories in the Netherlands. The gene package comprised the next-generation sequencing panel designed for vision disorders, including comparable sets of investigated genes across all three ophthalmogenetic laboratories.[18–20] Variants were classified into pathogenic (class 5), likely pathogenic (class 4), variant of uncertain significance (class 3), likely benign (class 2), or benign (class 1), in accordance with the American College of Medical Genetics and Genomics (ACMG) guideline.[21] A confirmed genotype was considered if variants in IRD-associated genes were found and could be classified as causative according to the ACMG guideline. Analysis of the *OPN1LW/OPN1MW* gene cluster was performed in the ophthalmogenetic lab of the Radboud UMC using a method described and developed by Haer-Wigman et al.[22] This developed assay is capable of detecting a wide range of pathogenic variants within this cluster, achieved through a combination of copy number analysis and long-read sequencing.

Since the gene package for vision disorders continued to be updated annually, we performed a comprehensive re-review in 2022 in patients who initially had inconclusive or missing genetic data during the original data collection period. This aimed to include updated genetic examinations and/or reanalyses of genetic data using an updated gene panel.

Statistical Analyses

We analyzed the frequencies of IRD phenotypes and disease-causing genes. Demographic measurements were listed using the median (interquartile range [IQR]). All analyses were performed using IBM SPSS statistics (version 28.0.1.0 (142); SPSS, Inc., Chicago, IL, USA). Descriptive horizontal

bar plots and vertical bar plots were created using R (R version 4.0.5; R Project for Statistical Computing, Vienna, Austria). To estimate the prevalence of IRD among individuals up to age 21 years in the Netherlands, the following formula was utilized: total IRD/total population * 100,000. As of January 1, 2020, 3,775,257 individuals up to the age of 21 years were living in the Netherlands.[23]

Results

Cohort Characteristics

In total, 624 patients from the RD5000 national database were eligible for this study. Median age at time of registration was 13 years (IQR, 9–16), and 63% were male patients. Genetic analyses were performed in 473 patients, of whom a genetic cause was found in 360 patients (76%). Pathogenic variants were found in 78 different genes. Table 1 shows the demographic data of our cohort. The estimated prevalence of IRD among individuals up to age 20 years in the Netherlands was 17 per 100,000.

Clinical Phenotypes

In total, 30 different IRD phenotypes were present, of which 87% of the phenotypes were nonsyndromic IRD and 13% were syndromic IRD (Fig. 1). The top 10 most frequent phenotypes were RP ($n = 123$, 20%), Leber congenital amaurosis (LCA) ($n = 97$, 16%), X-linked retinoschisis (XLRS) ($n = 64$, 10%), achromatopsia ($n = 63$, 10%), cone dystrophy ($n = 47$, 8%), congenital stationary night blindness (CSNB) ($n = 47$, 8%), cone-rod dystrophy ($n = 31$, 5%), Best vitelliform macular dystrophy ($n = 23$, 4%), Usher syndrome ($n = 23$, 4%), and Bardet–Biedl syndrome ($n = 21$, 3%).

The age at diagnosis per phenotype is shown in Table 2. Patients with LCA had the lowest median age at diagnosis (1 year; IQR, 0–3). Patients with Bornholm eye disease had the highest median age at diagnosis (11 years; IQR, 6–16.5).

Table 1. Demographic Data

Characteristic	Value
Patients	624 (100)
Male	395 (63)
Age at registration, median (IQR), y	13 (9–16)
Different phenotypes, *n*	30
DNA available	473 (76)
DNA conclusive	360 (76)
Causative genes	78

Values are presented as number (%) unless otherwise indicated.

Table 2. Age at Diagnosis per Phenotype in Increasing Order of Age at Diagnosis

Diagnosis	Frequency*	Age at Diagnosis, Median (IQR), y
Leber congenital amaurosis	71	1 (0–3)
Alstrom syndrome	7	3 (1–4)
Achromatopsia	46	4 (3–7)
Joubert syndrome	5	5 (0.5–14.5)
X-linked retinoschisis	46	5 (2–8)
Congenital stationary night blindness	33	6 (3.5–9)
Best vitelliform macular dystrophy	18	6 (4–9)
Bardet–Biedl syndrome	13	6 (4–10)
Choroideremia	12	7.5 (3–11.6)
Retinitis pigmentosa	95	8 (5–12)
Cone-rod dystrophy	20	8 (6–12)
Cone-dystrophy	33	8 (5.5–13)
Stargardt disease	11	9 (8–11)
Usher syndrome	17	10 (3–15)
Bornholm eye disease	5	11 (6–16.5)

*Reported in this table are the phenotypes of which the age at diagnosis in at least five patients was registered in the RD5000 database.

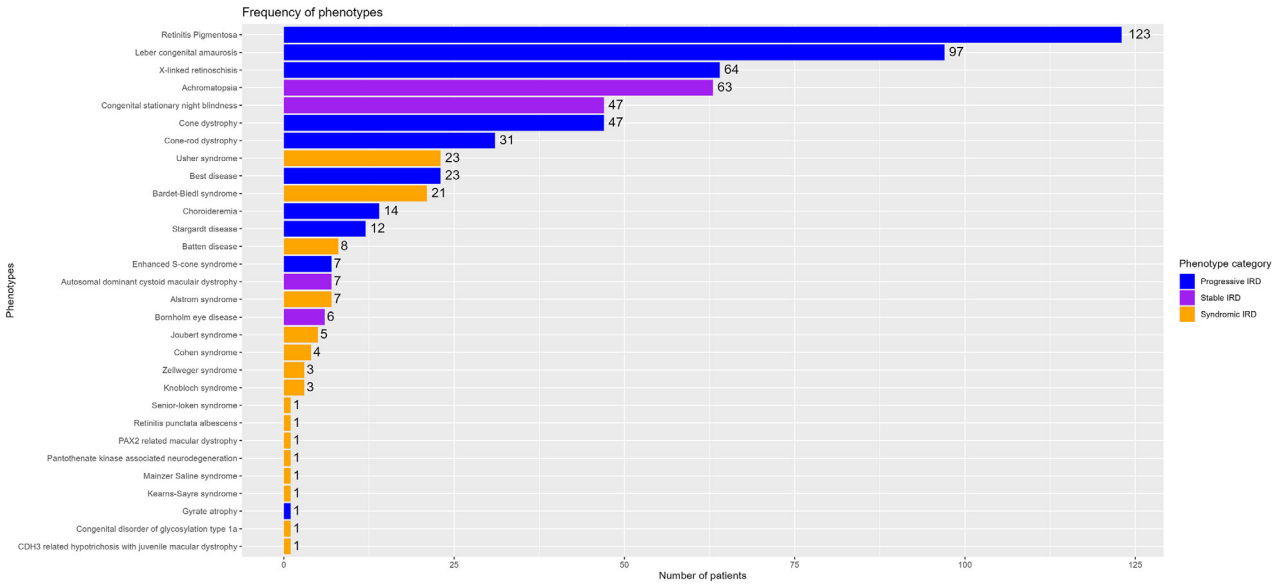

Figure 1. Frequencies of IRD phenotypes in patients ≤20 years old in the Netherlands. Colors represent IRD subgroups: *blue* = progressive IRD, *purple* = stationary IRD, and *orange* = syndromic IRD.

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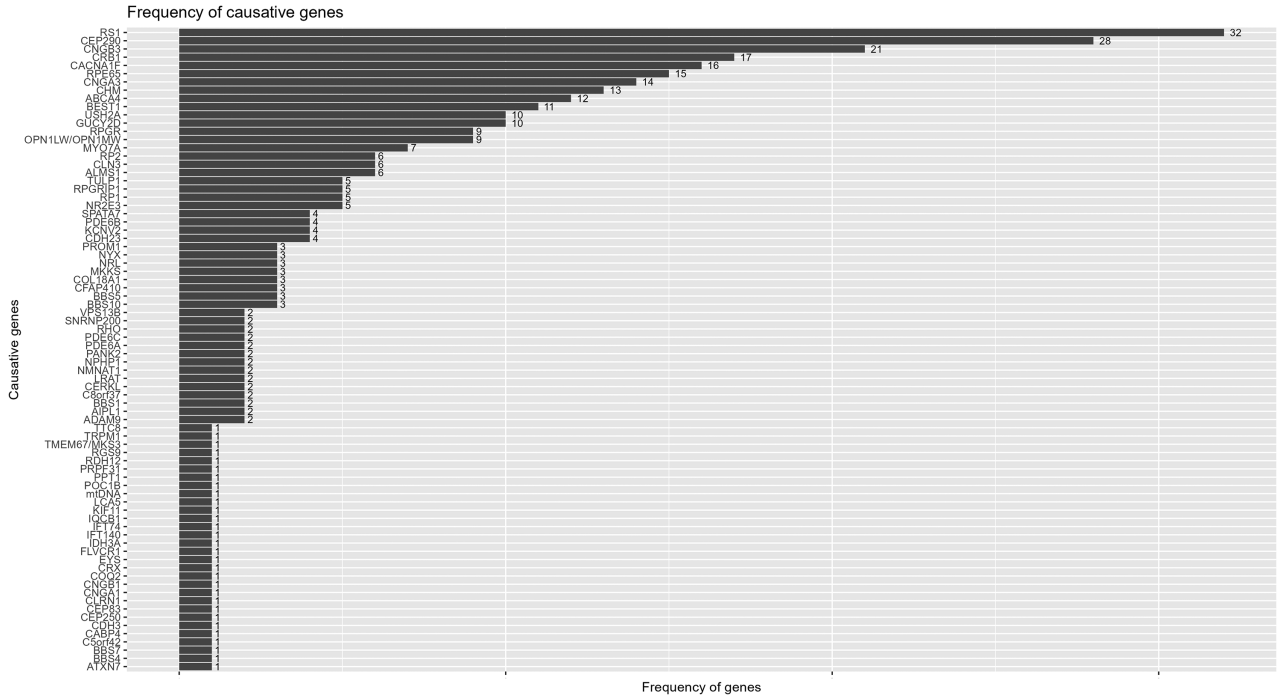

Figure 2. Frequencies of identified genetic causes of IRD in patients ≤20 years old in the Netherlands. mtDNA, mitochondrial DNA.

Genetic Characteristics

Of 473 patients (76%), outcomes of genetic results were available. Of these patients, the genetic cause was identified for 360 (76%) patients. The top 10 most frequently disease-causing genes were *RS1* (n = 32, 9%, as a cause of XLRS), *CEP290* (n = 28, 8%, as a cause of LCA and RP), *CNGB3* (n = 21, 6%, as a cause of achromatopsia), *CRB1* (n = 17, 5%, as a cause of LCA and RP), *CACNA1F* (n = 16, 4%, as a cause of CSNB), *RPE65* (n = 15, 4%, as a cause of LCA), *CHM* (n = 13, 4%, as a cause of choroideremia), *CNGA3* (n = 13, 4%, as a cause of achromatopsia), *ABCA4* (n = 12, 3%, as a cause of Stargardt disease), and *BEST1* (n = 11, 3%, as a cause of Best vitelliform macular dystrophy). The frequencies of all identified disease-causing genes are presented in Figure 2. Supplement A shows a list of all genetic variants available in the RD5000 database for this cohort.

In 23 (6%) of these 360 patients, for whom the causative variant had not been identified in a first analysis, a subsequent reanalysis of genetic data resulted in a conclusive genetic result. Among these patients, the most frequent genetic causes were causative mutations in *RS1* (n = 3), *CACNA1F* (n = 2), *GUCY2D* (n = 2), and *OPN1LW/OPN1MW* (n = 2) (Table 3).

Figure 3 demonstrates various phenotypic groups (e.g., RP, LCA) with corresponding disease-causing genes when causative variants were found in more than one disease-causing gene.

In 310 of 360 (86%) of the genetically solved patients, the inheritance pattern was known. The pattern was autosomal recessive for 211 (58%) patients, autosomal dominant for 15 (4%) patients, X-linked for 83 (23%) patients, and mitochondrial for 1 (0%) patient, diagnosed with Kearns–Sayre syndrome.

Table 3. Frequencies of Genetic Causes and Phenotypes for Patients Who Received a Conclusive Genetic Result After Reassessment of the Data in 2022

Phenotype	Causal Gene	Frequency
X-linked retinoschisis	*RS1*	3
Bornholm eye disease	*OPN1LW/OPN1MW*	2
Congenital stationary night blindness	*CACNA1F*	2
Leber congenital amaurosis	*GUCY2D*	2
	CRB1	1
Cone dystrophy	*RP2*	1
	KIF11	1
Stargardt disease	*ABCA4*	1
Retinitis pigmentosa	*RP1*	1
	IDH3A	1
	FLVCR1	1
	CRB1	1
	PROM1	1
Enhanced S-cone syndrome	*NR2E3*	1
Achromatopsia	*CNGB3*	1
Bardet–Biedl syndrome	*BBS4*	1
Usher syndrome	*MYO7A*	1
	CDH23	1

In 22 of the 151 patients (15%) for whom no DNA analyses were performed, the genetic cause was known in the family. The most frequent genes in this group were *RS1* (n = 9) and *NRL* (n = 3).

Discussion

In this nationwide study of children with IRD in the Netherlands, RP and LCA were the most common overall pheno-

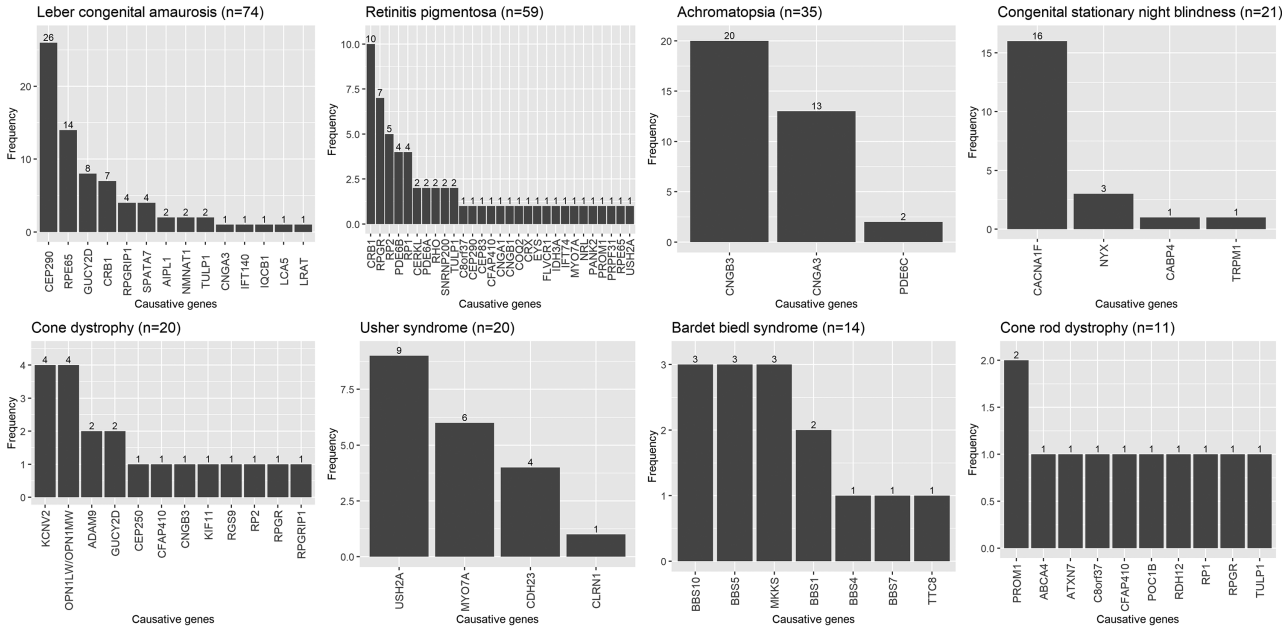

Figure 3. Frequency of disease-causing genes within each phenotypic group, considering IRD with multiple genes involved, with a focus on phenotypic groups with conclusive genetic results for over 10 patients.

types of progressive IRDs, while achromatopsia and CSNB were most prevalent among stationary IRDs. The predominant syndromic IRD in children was retinal degeneration as part of Usher syndrome. Genetic analysis revealed a causative variant in 76% of patients. Variants in *RS1*, as a cause of XLRS, and variants in *CEP290*, as a cause of RP and LCA, were the overall most common disease-causing genes and the most common disease-causing genes in progressive retinal dystrophies. Variants in *CNGB3*, as a cause of achromatopsia, and variants in *CACNA1F*, as a cause of CSNB, were the most common disease-causing genes in stationary IRDs. Usher syndrome was most often caused by variants in *USH2A* and *MYO7A*. These most frequent phenotypes and genetic causes can be important targets for the development of therapy.

To the best of our knowledge, child-focused studies on the frequencies of IRDs are limited. Bertelsen et al.[24] conducted a nationwide study in Denmark, revealing a 13 per 100,000 prevalence of IRD among children, with 57% nonsyndromic and 43% syndromic cases. LCA (31%) and RP (23%) were the most common IRDs. In our study, nonsyndromic IRD constituted 87%, with lower frequencies for RP (20%) and LCA (16%). Silveira et al.[25] reported that 17% of all Australian visually impaired children were diagnosed with IRD, with LCA (9%) and RP (9%) most frequently reported. Studies involving adults showed higher RP rates (23%–55%), potentially explaining our lower RP frequency in a cohort under 20 years, as the age of onset of RP can be beyond adolescence.[26–31] The higher LCA frequency in our cohort, compared to cohorts including adults, aligns with its early onset (before 5 years old).[32] Another explanation for the differences between children and adult cohorts in IRD presentation may be due to phenotypic clarity in children versus converging advanced-stage disease in adults, despite diverse genotypes. This affects diagnosis and treatment strategies, as phenotypic clues help interpret genetic findings. Moreover, conditions mimicking IRD, like posterior uveitis, are less common in children than adults.[33]

When comparing population studies, it is important to acknowledge that the prevalence of various IRDs and identified gene proportions can vary across populations, especially in cases with notable consanguinity.[15]

Our study reports a 76% diagnostic yield in genetic testing up to 2023, contrasting with Bertelsen et al.,[24] who reported a 42% diagnosis rate in 2011. The disparity is attributed to the continuous discovery of new causal genes and variants over the past decade, incorporated into annually updated gene panels for vision disorders.[34] Although the genetic data in our study were initially registered from 2017 to 2020, the genetic test could have been performed years earlier. Medical charts of patients without an identified genetic cause were reassessed in 2022 so as not to miss important genetic data. In our study, the diagnostic yield of the reanalysis of genetic data was 6%.

The increase in diagnostic yield could be attributed to novel gene–disease discoveries, updated clinical features, and improved bioinformatics tools. In 2016, 369 genes were analyzed in the gene package for vision disorders, compared to 510 genes in 2021.[35,36] This highlights the benefit of repeating genetic diagnostics if no causative genetic variant was initially identified, ideally every 5 years.

When examining genetic causes, frequent variants in Danish children were reported in *RPGR*, *RPE65*, and *MYO7A*.[24] In a Spanish cohort (adults and children) study, the most frequent mutated genes included *ABCA4*, *USH2A*, *RS1*, *CRB1*, and *RHO*.[37] A pediatric Irish cohort reported *RS1*, *CNGB3*, *ABCA4*, *RPGR*, and *NIX* as the most common genetic etiologies.[14] A Brazilian cohort study on children identified variants in *CEP290*, *RPE65*, *CRB1*, and *RPGRIP1* genes as common genetic causes for LCA or early-onset retinal dystrophy.[38] *ABCA4*, *KCNV2*, and *CRB1* were the most frequent mutated genes in childhood-onset IRD in Emirati patients.[15] In our study, *RS1*, *CNGB3*, *CRB1*, *RPE65*, *CEP290*, and *ABCA4* were among the frequently registered genetic causes. When focusing on syndromic IRD, especially Usher syndrome, high frequencies of causative mutations

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in *USH2A* and *MYO7A* are consistent with large cohorts of both adult and pediatric Usher syndrome.[39] The identified genetic causes exhibit some overlap with findings elsewhere, but they also underscore the importance of region-specific genetic considerations in comprehensively addressing the diversity in IRD causes. The relatively higher incidence of *RPE65* mutations might be attributable to increased referrals following the approval of voretigene neparvovec for IRD gene therapy.[9] However, in the Netherlands, all children with IRD are mostly treated at one of the participating centers of the RD5000. Nevertheless, the instinct to refer a patient with an *RPE65* mutation can be higher if the patient was still under treatment in a different center, which could be due to personal preference or logistical reasons.

Among strengths of our study are the completeness and uniformity of our data collection, as well as the extensive genetic workup. However, limitations may include an overrepresentation of follow-up data for patients with XLRS due to an ongoing natural course of disease study.[40] Furthermore, as the RD5000 database is utilized for multiple nationwide studies with various research aims, some cases analyzed may have been previously reported in other studies using pediatric and adult data from the RD5000 database.[41–50]

Notably, the frequency of Usher syndrome appears comparable to Bardet–Biedl syndrome, contrary to expectations based on perceived prevalence in the population.[51,52] This observed bias may be attributed to the relatively modest sample sizes, causing noticeable discrepancies. Additionally, it is crucial for children to receive treatment in a tertiary medical facility for inclusion in the RD5000 database. Not meeting this requirement, whether still under secondary care or unrecognized as having an IRD, may result in underestimating the frequencies. For the RD5000 database, each center bears its own responsibility to input data on their patients. In order to correct for the potential bias of underestimating the frequencies due to not every treated patient being registered, patients for this study were actively registered over a period of 2 years. Furthermore in the Netherlands, six of the participating centers are located in the highly urbanized and ethnically diverse western region of the Netherlands, while two centers are located in rural regions with a predominantly white ethnicity, as well as responsible for a larger geographic area.

Unfortunately, we were not able to study visual function. Many children in the database were very young, which hampered reliably measuring visual acuity. Prospective studies will be necessary for evaluation of the natural course of both common and rare phenotypes, taking into account the potential differences between causal genes. Reliably measuring best corrected visual acuity (BCVA) in children, taking into account age-dependent visual acuity tests and motivational factors, remains challenging, emphasizing the importance of repetitive BCVA measurements before drawing conclusions.[53]

Advancements in molecular genetics have enhanced our understanding of inherited retinal dysfunction mechanisms, paving the way for gene-directed therapeutic strategies. Notably, voretigene neparvovec (Luxturna) is now available for treating biallelic *RPE65*-related IRD.[9] Clinical trials, including those up to phase 3, are under way globally for X-linked RP caused by *RPGR* variants, with ongoing treatment in the Netherlands and elsewhere.[54–56] These developments mark the significance of comprehending the disease course for timely intervention before complete vision loss occurs.

In conclusion, the RD5000 database is important for identifying Dutch patients suitable for future gene therapies. While prospective natural history studies are vital for accurate prognostication and optimizing therapeutic timing, they are time-consuming, expensive, and logistically challenging. Retrospective follow-up studies on rare IRD patient groups, like those enabled by RD5000, remain highly valuable due to feasibility constraints.

Acknowledgments

Supported by Uitzicht 2015-30 (ODAS, Oogfonds, Retina Fonds, Bartimeus Sonneheerdt), Erasmus MC fellowship 2021 (VJMVV), Uitzicht 2019-18 (Landelijke Stichting Blinden en Slechtzienden, Algemene Nederlandse Vereniging Ter Voorkoming van Blindheid), and Henkes Stichting. The sponsor or funding organization had no role in the design or conduct of this research.

Disclosure: **P.A.T. Heutinck**, None; **L. Ingeborgh van den Born**, None; **M. Vermeer**, None; **A.I. Iglesias Gonzales**, None; **C.B. Hoyng**, None; **J.W.R. Pott**, None; **H.Y. Kroes**, None; **M.J. van Schooneveld**, None; **C.J.F. Boon**, None; **M.M. van Genderen**, None; **A.S. Plomp**, None; **Y. de Jong-Hesse**, None; **M.B. van Egmond-Ebbeling**, None; **L.H. Hoefsloot**, None; **A.A. Bergen**, None; **C.C.W. Klaver**, None; **M.A. Meester-Smoor**, None; **A.A.H.J. Thiadens**, None; **V.J.M. Verhoeven**, None

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