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Characterizing the Genetic Basis for Inherited Retinal Disease: Lessons Learned From the Foundation Fighting Blindness Clinical Consortium's Gene Poll

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Purpose. The Foundation Fighting Blindness (FFB) Consortium is a collaboration of 41 international clinical centers that manage patients affected with inherited retinal diseases (IRDs). The annual Consortium gene poll was initiated in 2020 to capture the genetic cause of disease in patients with IRD and associated clinical practices of Consortium sites. Data from the 2022 gene poll are reported here.

Methods. In 2022, academic, private practice, and government ophthalmology clinics that are members of the Consortium centers were polled to identify per-case IRD genetic causality from a list of 387 syndromic and nonsyndromic IRD genes. The survey also assessed how genetic testing was obtained and clinical practices of the sites.

Results. Thirty centers responded and reported genetic data from 33,834 patients (27,561 families). Disease-causing variants were reported in 293 of 387 genes. The most common genetic etiologies were *ABCA4* (17%), *USH2A* (9%), *RPGR* (6%), *PRPH2* (5%), and *RHO* (4%). The top 100 genes accounted for the genetic cause of disease in 94.4% of patients. Two-thirds of the centers had at least one genetic counselor. In the 21 US sites, genetic testing was commonly obtained through sponsored programs (95%, FFB-My Retina Tracker Programs or Spark-ID Your IRD), whereas in the 9 non-US sites, genetic

testing was commonly obtained using either patient- or public health system-funded testing pipelines. Clinical work-up of patients with IRD most commonly included updating history, eye examination, and optical coherence tomography.

Conclusions. This report provides the largest assessment of genetic causality in the IRD patient population across multiple continents to date.

Keywords: inherited retinal degenerations, genotype, retinitis pigmentosa, genetic testing

Inherited retinal diseases (IRD) are a diverse group of more than 50 conditions associated with multiple syndromic and nonsyndromic phenotypes.[1,2] These conditions are characterized by a primary or secondary degeneration or dysfunction of the photoreceptors, often associated with progressive vision loss that may cause legal blindness. The most common IRD is retinitis pigmentosa (RP), although other conditions such as Stargardt disease, cone/cone–rod dystrophies, and Usher syndrome, are also frequently seen. It is estimated that IRDs affect approximately 1 in 3,450 individuals with significant disease-specific and geographic variability.[3] However, given the limited availability of providers with expertise in accurately diagnosing inherited retinal degenerations, their true prevalence may be unknown.[4]

Although approximately 270 genes are generally accepted to be associated with IRDs, additional candidate genes are being identified continuously and novel phenotype associations with existing syndromic and nonsyndromic genes continue to be uncovered.[5] The addition of genes from these latter categories to those that are well-established results in more than 387 different genes that may be associated with this group of conditions (Supplementary Appendix A). The extensive clinical and genetic heterogeneity associated with this group of genes and diseases poses challenges for clinicians and scientists developing treatments, as a single gene may be associated with multiple phenotypes and associated with more than one inheritance pattern.[1,5,6]

Genetic testing for IRDs is now considered to be standard of care in establishing a diagnosis for patients with IRDs.[7] Improvements in genetic testing methodology over time, such as the development of next-generation sequencing, identification of novel genes, and implementation of copy number variant analysis, have improved the ability to determine the genetic basis for disease, such that detection rates for determining the genetic basis for disease in patients with IRD is approximately 52% to 76%.[8–13] This testing is an essential complement to clinical examination for accurately determining the risks for other members of the family, and determining eligibility for current and future gene-based treatments.[14] Testing may take place through commercial testing laboratories, site-based academic laboratories, or research programs. However, cost and insurance coverage can be a factor preventing access altogether or requiring patients who are able to self-fund testing.[15] In the United States, several sponsored testing programs have been available in recent years offering genetic testing to patients with IRDs expanding access to testing to a larger group of patients: the My Retina Tracker (MRT) Open Access Genetic testing program (sponsored by the Foundation Fighting Blindness [FFB]), the ID Your IRD Program (sponsored by Spark Therapeutics, discontinued in December of 2022), and the Inherited Retinal Disease Program (sponsored by Invitae)—offer no-cost genetic testing to patients with IRDs.[15–17] In addition to the MRT Open Access clinical genetic testing program, FFB supports an MRT research genetic testing program.

Understanding the genetic basis for these conditions in large global populations is essential for understanding disease burden as well as for developing treatments for this patient cohort. The Consortium was established in 2016 to conduct clinical studies in patients with IRDs with the goal of accelerating the development of treatments.[18] The combined 41 clinical centers (in 2022) from 13 countries on four continents provide a valuable resource for studying patients affected with these conditions. The gene poll is a survey administered annually to Consortium sites to capture a snapshot of the number of patients with mutations in specific IRD genes. This gene poll provides valuable information to shape the course of clinical studies within the Consortium and adds to the IRD community's understanding of the genetic basis for disease in an international cohort.

Methods

Design and Sample Selection

Forty-one Consortium sites were invited to participate in the 2022 gene poll. Individual sites were asked to tally the cumulative number of patients and families seen at that site affected with IRDs owing to disease-causing (pathogenic or likely pathogenic) variants in 1 of the 387 different genes known to be implicated in syndromic and nonsyndromic IRDs. The list of IRD genes was compiled by identifying genes associated with IRDs listed on RetNet, the Retinal Information Network, and from genes tested on common commercial next generation sequencing IRD panels. Genes were excluded from the gene poll analysis if they were not associated with IRDs or not associated with Mendelian or mitochondrial inheritance. Genes were still included in the poll even if they are still considered to be candidate IRD genes without definitive evidence. Sites were asked to tally all patients (active and historical) on a gene-by-gene basis in which either two pathogenic or likely pathogenic variants were identified in an autosomal recessive gene, or at least a single pathogenic or likely pathogenic variant was identified in an X-linked, autosomal dominant, or mitochondrial gene. Segregation analysis was not required to have been performed for an individual to be included. The survey also included site-specific questions on methods of genetic testing and other clinical practices. Respondents were asked how genetic testing was obtained. Throughout the paper, genetic testing obtained through either the FFB MRT Open Access genetic testing program or FFB-sponsored MRT research genetic testing program are collectively called the MRT genetic testing program, and sponsored genetic testing refers to both the MRT genetic testing program and ID your IRD.

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Statistical Analysis

The number of patients and families with mutations in each gene were calculated from the survey data and ranked by prevalence. Cumulative patient and family tallies were calculated for the top 5, 20, 100, and 193 (half) of genes analyzed. The top five genes by region (North America, South America, and Europe) were analyzed. Site-specific data on genetic testing, insurance, and clinical practices were tabulated and analyzed using bar graphs. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Genetic Cause of Disease

Thirty of the 41 active Consortium sites responded to the 2022 gene poll survey, including 21 sites in North America (all in the United States), 6 sites in Europe, 2 sites in South America (both in Brazil), and 1 site in Asia (Israel) (Fig. 1). Respondents reported 33,834 patients from 27,561 families with disease-causing variants in 293 of the 387 genes. No patients were identified as having disease-causing variants in 94 genes (Table 1). Eighty-six of the disease-associated genes were found in 50 or more patients, 50 were found in 20 to 49 patients, 67 were found in 5 to 19 patients, and 90 were found in 1 to 4 patients (Table 2). The five most common causes of IRD were *ABCA4*, *USH2A*, *RPGR*, *PRPH2*, *and RHO*, accounting for 17%, 9%, 6%, 5%, and 4% of disease burden, respectively. Together disease-causing variants in these 5 genes were reported in 13,850 patients (41%) and 11,064 families (40%). Although disease-causing variants in these five genes were most common in the European and US populations, in Brazil *ABCA4* (21%), *USH2A* (8%), *RHO* (4%), *EYS* (4%), and *RPGR* (4%) were the five most common disease-associated genes (Table 3). Gene tallies for Asia are not reported as these are based on only one site in Israel. The 193 (50%) most frequent disease-associated genes were reported in 33,588 patients (99%) and 27,561 families (99%) (Tables 4 and 5).

Table 1. Disease-Associated Genes not Determined as Being Associated in any IRD Patient in the 2022 Gene Poll ($N = 94$)

ACBD1	*CISD2*	*GPR125*	*MT-RNR2*	*MT-TW*	*PSEN1*
ACBD5	*CLN5*	*HKDC1*	*MT-TC*	*MT-TY*	*SIX6*
AHR	*CLN8*	*HMX1*	*MT-TD*	*NEUROD1*	*SMARCA4*
ATOH7	*COL9A2*	*IFT43*	*MT-TE*	*OPN1SW*	*TCTN1*
B9D1	*CRB2*	*IFT80*	*MT-TF*	*PDE6D*	*TCTN3*
B9D2	*DACT2*	*INVS*	*MT-TG*	*PEX3*	*TEAD1*
BBIP1	*DDR1*	*KIAA0556*	*MT-TH*	*PEX5*	*TMED7*
C2CD3	*DHX32*	*KIF3B*	*MT-TI*	*PEX10*	*TMEM67*
C5AR2	*DNAJ17*	*LRRTM4*	*MT-TK*	*PEX11B*	*TMEM107*
CCDC188	*DSCAML1*	*LZTFL1*	*MT-TL2*	*PEX14*	*TMEM138*
CCT2	*ENSA*	*MIR204*	*MT-TM*	*PEX16*	*TMEM216*
CEP19	*ESPN*	*MT-ATP8*	*MT-TN*	*PEX19*	*TRIM32*
CEP41	*EXOSC2*	*MT-CO1*	*MT-TQ*	*PGK1*	*USP45*
CEP83	*FBN3*	*MT-CO2*	*MT-TR*	*PISD*	*WDPCP*
CEP104	*GDF6*	*MT-CO3*	*MT-TS1*	*PPP2R3C*	
CEP120	*GPR45*	*MT-ND2*	*MT-TT*	*PROS1*	

Clinical Practices

Of the 30 sites participating in the survey, 20 (67%) participated in the MRT Genetic Testing Program. Of the remaining ten sites, 9 (90%) were not located in the United States and therefore not eligible to participate in the MRT Genetic Testing Program. Of the 30 sites, 3 (10%) used only site-specific laboratories, 5 (17%) used site and commercial laboratories, and the remaining 22 (73%) used a combination of commercial, sponsored, site, or research laboratories to obtain genetic data. Among the 21 sites in the United States, 20 (95%) incorporated sponsored programs to obtain genetic data. Of the 21 sites (US and non-US) that used sponsored programs, 11 (52%) used MRT Research, 14 (67%) used MRT open access, and 15 (71%) used ID your IRD. In non-US sites, all sites had the ability to obtain genetic data using site-based laboratories (Fig. 2). Of the 21 sites located in the United States, 16 (71%) reported that all or most of the cost of patient's genetic testing was covered by FFB with the remaining percentage covered by public or private health insurance, private pay, or other methods. Of the nine sites using other methods to cover the cost of

Figure 1. Map of Consortium sites that participated in the 2022 gene poll.

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Table 2. Disease-Associated Genes Determined as Being Associated in Patients With IRD in the 2022 Gene Poll ($N = 293$)

Gene	Patient Count	Gene	Patient Count	Gene	Patient Count
ABCA4	5878	*ND1 (MT-ND1)*	76	*NDP*	23
USH2A	2918	*WFS1*	75	*NPHP4*	23
RPGR	1962	*MT-TL1*	72	*BBS7*	22
PRPH2	1582	*RDH5*	72	*CC2D2A*	22
RHO	1510	*PDE6C*	69	*DRAM2*	22
CHM	1015	*RLBP1*	69	*PEX1*	22
EYS	919	*IQCB1 (aka NPHP5)*	67	*TSPAN12*	22
BEST1	857	*TOPORS*	67	*LAMP2*	21
CRB1	708	*LCA5*	66	*PHYH*	21
PRPF31	689	*SAG*	66	*RIMS1*	21
RS1	686	*EFEMP1*	65	*SLC24A1*	21
RP1	668	*OAT*	64	*BBS5*	20
CNGB3	651	*LRAT*	61	*BBS9*	20
CNGA3	510	*VPS13B*	60	*CACNA2D4*	20
MYO7A	449	*BBS2*	59	*C8orf37*	19
RPE65	437	*HGSNAT*	59	*CTNNA1*	19
CEP290	412	*LRP5*	59	*CWC27*	19
CACNA1F	387	*SPATA7*	58	*PRPS1*	19
PROM1	377	*KLHL7*	57	*RBP3*	19
NR2E3	367	*AHI1*	56	*MKKS*	18
GUCY2D	362	*DHDDS*	54	*CEP250*	17
RDH12	357	*TTLL5*	54	*MT-ATP6*	17
RP2	319	*C21orf2 (aka CFAP410)*	51	*PNPLA6*	17
PDE6B	313	*ND6 (MT-ND6)*	51	*ARL6*	16
BBS1	311	*RP9*	50	*ATF6*	16
CRX	276	*ABCC6*	48	*CNNM4*	16
PDE6A	243	*KIZ*	47	*GNAT2*	16
CERKL	242	*MFRP*	47	*IFT172*	16
FAM161A	213	*FLVCR1*	46	*PRPF6*	16
PRPF8	208	*NRL*	46	*RGR*	16
CNGB1	187	*CDH3*	45	*ARSG*	15
IMPG2	185	*KIF11*	44	*PDE6G*	15
RP1L1	184	*ACO2*	43	*PRCD*	15
MERTK	179	*C1QTNF5*	43	*TUB*	15
SNRNP200	174	*MFSD8*	43	*USH1G*	15
IMPDH1	170	*PRDM13*	40	*SEMA4A*	14
NYX	160	*CEP78*	39	*ZNF408*	14
CDHR1	158	*COL18A1*	39	*GNAT1*	13
CLN3	150	*IMPG1*	38	*ITM2B*	13
TULP1	144	*FZD4*	36	*KCNJ13*	13
KCNV2	142	*GRM6*	36	*LAMA1*	13
ADGRV1	138	*HK1*	36	*OTX2*	13
CDH23	134	*BBS12*	35	*PEX6*	13
TRPM1	133	*POC1B*	32	*PITPNM3*	13
C2orf71 (aka PCARE)	131	*GPR179*	31	*RAB28*	13
AIPL1	127	*WDR19*	31	*RD3*	13
RPGRIP1	120	*ABHD12*	30	*SSBP1*	13
GUCA1A	113	*OPN1LW only*	30	*GRK1*	12
CLRN1	109	*INPP5E*	29	*AGBL5*	11
PCDH15	109	*RAX2*	28	*ARL2BP*	10
MAK	108	*ATXN7*	27	*CAPN5*	10
TIMP3	108	*ELOVL4*	27	*OFD1*	10
CYP4V2	106	*NPHP1*	26	*PAX2*	10
ALMS1	99	*ADAM9*	25	*TTC8*	10
CNGA1	91	*VCAN*	25	*TUBB4B*	10
BBS10	88	*BBS4*	24	*IDH3A*	9
IFT140	86	*CABP4*	24	*MTTP*	9
NMNAT1	85	*JAG1*	24	*TUBGCP6*	9
PRPF3	83	*REEP6*	24	*LRIT3*	8
USH1C	81	*ROM1*	24	*RBP4*	8
COL2A1	80	*COL11A1*	23	*SDCCAG8*	8

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Table 2. Continued

Gene	Patient Count	Gene	Patient Count	Gene	Patient Count
HARS	7	*ARL13B*	3	*TREX1*	2
MVK	7	*COL9A1*	3	*TTC21B*	2
P3H2	7	*CSPP1*	3	*TTPA*	2
TMEM231	7	*CTC1*	3	*ASRGL1*	1
TRNT1	7	*CTNNB1*	3	*C12orf65*	1
ARHGEF18	6	*MPDZ*	3	*CIB2*	1
ARL3	6	*MT-TS2*	3	*CLCC1*	1
GNB3	6	*NPHP3*	3	*CLN6*	1
MKS1	6	*PLA2G5*	3	*COL9A3*	1
OPN1MW only	6	*POC5*	3	*COQ2*	1
RCBTB1	6	*SLC66A1*	3	*GNPTG*	1
FSCN2	5	*TRAF3IP1*	3	*IDH3B*	1
KIAA1549	5	*UNC119*	3	*IFT27*	1
PANK2	5	*ZNF513*	3	*IFT74*	1
PEX7	5	*ADIPOR1*	2	*IFT88*	1
PLK4	5	*AMACR*	2	*KIAA0753*	1
PRPF4	5	*ARMC9*	2	*MT-CYB*	1
RGS9	5	*C5orf42 (aka CPLANE1)*	2	*MT-ND3*	1
SCAPER	5	*CTSD*	2	*MT-TA*	1
SRD5A3	5	*DHX38*	2	*MT-TV*	1
ADAMTS18	4	*DTHD1*	2	*NEK2*	1
AFG3L2	4	*GRN*	2	*PEX12*	1
CA4	4	*IFT81*	2	*PEX2*	1
CEP164	4	*KIF7*	2	*RDH11*	1
CLUAP1	4	*MAPKAPK3*	2	*RHBDD2*	1
COL11A2	4	*MT-RNR1*	2	*RRM2B*	1
DFNB31 (aka WHRN)	4	*MT-TP*	2	*SAMD11*	1
DYNC2H1 (aka WDR34)	4	*NAGLU*	2	*SCLT1*	1
GUCA1B	4	*ND5 (MT-ND5)*	2	*SGSH*	1
KIAA0586	4	*PCYT1A*	2	*SLC39A12*	1
MMACHC	4	*PDE6H*	2	*SLC4A7*	1
NBAS	4	*PEX13*	2	*SLC7A14*	1
POMGNT1	4	*PEX26*	2	*SPP2*	1
PPT1	4	*SLC25A46*	2	*TCTN2*	1
RGS9BP	4	*SLC37A3*	2	*TLCD3B*	1
RPGRIP1L	4	*TMEM237*	2	*ZNF423*	1
TUBGCP4	4	*TPP1*	2		

patients' genetic testing, 5 (56%) used sponsored programs (ID Your IRD/industry) to cover genetic testing costs of some patients. Of the nine sites located outside the United States, 6 (67%) reported that all or most of the cost of patient's genetic testing was covered by public or private health insurance or other methods including patient self-pay, research funding, and sponsored testing. Of the seven sites using other methods to cover the cost of patients' genetic testing, 3 (43%) used research funding to cover genetic testing in most patients (Fig. 3). At 20 sites (67%), most patients had received comprehensive gene panel testing within the past 5 years. In 3 sites (10%), this was true for some patients and in 7 (23%), this was true for all patients.

Twenty sites (67%) had a genetic counselor in clinic to work with patients with IRD. IRD patient visits were carried out annually in 15 sites (50%), every 2 years in 10 (33%), every 3 years in 3 (10%), and as needed in 2 (7%). Twenty-two of the 30 sites (73%) reported that more than 76% of patients' examinations were covered by insurance, 5 (17%) reported that between 51% and 75% of patients' examinations were covered by insurance, and 2 (7%) reported that less than 25% of patients' examinations were covered by insurance. The most frequent examination components for follow-up and new patient evaluations (carried out in more than 90% of sites), included updating patient history, performing an eye examination and SD-OCT. The least

Table 3. Top 5 Genes Overall and by Region in 2022

ALL (30 Sites) *N* = 33,834	United States (21 Sites) *N* = 13,445	BRAZIL (2 Sites) *N* = 3,573	EUROPE (6 Sites) *N* = 14,720
ABCA4 (17%)	*ABCA4* (16%)	*ABCA4* (21%)	*ABCA4* (18%)
USH2A (9%)	*USH2A* (9%)	*USH2A* (8%)	*USH2A* (9%)
RPGR (6%)	*RPGR* (7%)	*RHO* (4%)	*RPGR* (5%)
PRPH2 (5%)	*PRPH2* (5%)	*EYS* (4%)	*PRPH2* (5%)
RHO (4%)	*RHO* (5%)	*RPGR* (4%)	*RHO* (4%)

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Table 4. Cumulative Patient Tallies ($N = 387$ Total Genes)

Top Genes	Cumulative No. of Patients	Cumulative % of Patients
Top 5 genes	13,850	40.9%
Top 20 genes	22,982	67.9%
Top 100 genes	31,953	94.4%
Half (193) genes	33,588	99.3%

Table 5. Cumulative Family Tallies ($N = 387$ Total Genes)

Top Genes	Cumulative No. of Families	Cumulative % of Families
Top 5 genes	11,064	40.1%
Top 20 genes	18,583	67.4%
Top 100 genes	25,993	94.3%
Half (193) genes	27,332	99.2%

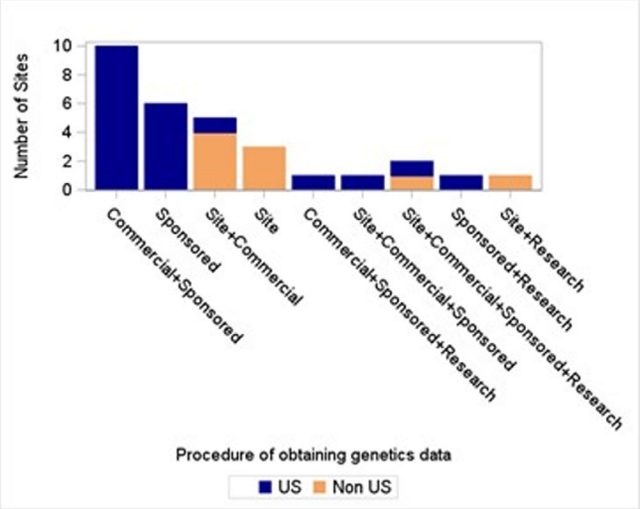

Figure 2. Site-reported methods of obtaining genetics data on patients in the United States and outside the United States.

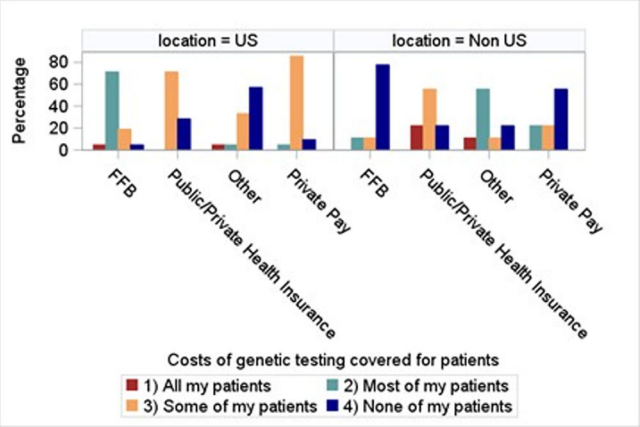

Figure 3. Cost of genetic testing covered for patients for sites located in the United States and outside the United States.

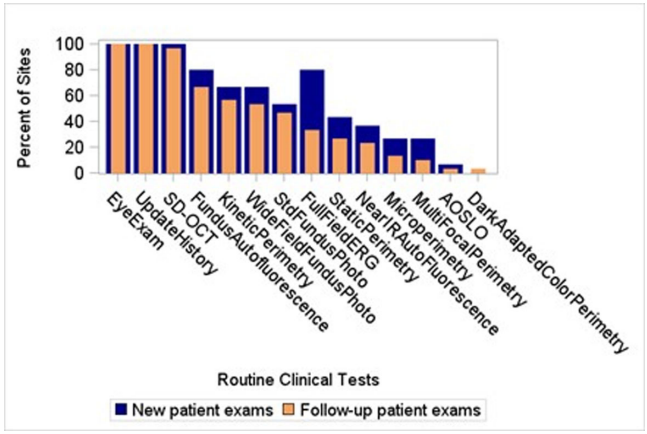

Figure 4. Routine clinical tests for new and follow-up patients. AOSLO, adaptive optics scanning laser ophthalmoscopy; FullField-ERG, full-field ERG.

frequent examination components included dark-adapted color perimetry and adaptive optics scanning laser ophthalmoscopy (Fig. 4) The majority of clinical sites perform (>75%) seven examination elements at new patient visits. These included eye examination, history update, kinetic perimetry, SD-OCT, fundus autofluorescence, and wide-field fundus photography, and full-field ERG. Most centers performed only eye examinations, history updates, SD-OCT imaging, and fundus autofluorescence imaging during return visits.

Discussion

Understanding the genetic basis for disease in patients affected with IRDs is an essential aspect of advancing management of these conditions. Moreover, understanding the clinical practices across diverse international IRD centers highlights the clinical needs and limitations of these practice settings. The data from the Consortium Gene Poll is uniquely positioned to provide insight on both topics.

Previous analyses of the genetic basis of disease have focused primarily on understanding genetic etiologies within a single country. Although the top genes within these studies have remained fairly consistent with *ABCA4* and *USH2A* identified as the two most common causes of disease across multiple studies, additional common causative gene defects may vary based on ethnic region.[9,10,19] The same pattern was seen within the present study, in which pathogenic variants in *ABCA4*, *USH2A*, and *RHO* were consistently identified as the most common causes of disease in the United States, Brazilian, and European sites, but *PRPH2*, *EYS*, and *CEP290* were only identified as top five causes of disease in one or two of the three geographic regions.

These gene poll data also confirm that despite the large number of genes associated with IRDs, the majority of cases are caused by variants in only a few genes. The top five genes across all sites (*ABCA4*, *USH2A*, *RPGR*, *PRPH2*, and *RHO*) account for disease burden in 40.5% of patients, the top 20 genes account for 67.7% of the disease burden, and the top one-half of the genes account for 99.2% of the disease

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burden. This pattern is similar to what others have found, confirming that, although numerous genes have been identified that cause these conditions, the majority (68%) can be explained by disease-causing variants in just 20 genes.[19] Despite this fact, broad IRD panels remain important in identifying genetic diagnoses for the greatest number of patients, as exemplified by the nearly 11,000 individuals in this cohort who have a genetic cause of disease in other than 1 of the top 20 genes.

Because genetic testing is considered standard of care for patients with IRDs, it is essential to understand current practices and limitations, particularly with regard to genetic counselors. The data from our study indicate that 67% of sites had a genetic counselor. Because genetic counselors are able to both facilitate the genetic testing and counsel on the results of testing, they can serve as an important part of care for these patients. The high proportion of Consortium sites, which are specialized in the care of patients with IRD, with genetic counselors is not representative of general ophthalmology clinics, or even general retina clinics. Although there are numerous genetic counselors in some countries, this expertise is not available in all countries.[20] Moreover, there are a limited number of counselors who specialize in ophthalmology. As genetic testing technologies evolve and more gene-specific treatments become available, developing a larger global contingency of genetic counselors with expertise in IRDs will become increasingly important for this patient population.

Genetic testing should be offered to all patients with IRD to assess the risk for family members, provide counseling, and optimize management, including the potential for gene-based treatment. Yet, patients may not always be able to access genetic testing for financial reasons. Although insurance may cover the cost of testing, this insurance coverage may vary from country to country, between insurance providers, and even between patients with the same insurance.[21] If not covered by insurance providers, patients may need to self-pay or seek the resources of other programs, such as sponsored testing or research genetic testing. One study was able to demonstrate that access to sponsored research genetic testing increased the rate of genetic testing for patients with IRDs by 29%.[15] In our study, 20 of 21 sites within the United States used sponsored genetic testing programs to collect genetic data and all sites indicated that all or most of their genetic testing was supported by sponsored testing programs. In contrast, the non-US sites indicated that all or most of their patients obtained genetic testing through public or private health insurance or other methods, such as research agencies. Access to genetic testing will continue to be an important part of care for patients with IRDs.

Finally, our study gathered information on clinical tests performed at both new and return patient visits. Recommendations have been published regarding assessments to be performed at clinical visits in patients with IRDs.[22] Although the majority of Consortium sites follow these recommendations, there can be slight variability in testing performed based on equipment availability and practice preferences among the physicians. The number of tests performed indicates the complexity involved in caring for patients affected with IRDs.

Because the data were gathered independently and in a deidentified manner from multiple clinic sites, limitations do exist within the nature of the data. Namely, the genetic data gathered from any clinic depend on a clinician or even a database maintaining complete and comprehensive information on genetic basis for disease within their clinic population, as well as the genetic testing strategy. Patients who had visits to multiple IRD clinics would be counted more than once and family relationships may not be known for family members visiting different IRD clinics. The retrospective nature of the study also means that genetic testing was not performed in a consistent way with varying genes and methodologies included on testing panels. For example, if a panel did not include mitochondrial genes, individuals with those genes as a cause of disease might be underrepresented in the cohort. Finally, IRD clinics may not be equally accessible to patients from all demographic backgrounds, and the results presented under-represent the genetic characteristics of patients with limited access to the expertise available at the IRD centers included in this study.

Although the data presented here represent genetic data from IRD clinics across multiple countries and several continents, there are regions of the world that are not represented in the data. Specifically, the Consortium does not currently have any sites in Africa and minimal representation in Asia. Previous genetic studies from these regions have demonstrated some overlap with most common causes of disease in the Consortium data, but there are also genetic causes of disease which are more common in these additional regions.[23–26]

The present study is the largest study on the genetic basis of patients affected with IRDs to date. This information is essential to promote the understanding of these conditions, not only within the Consortium, but for the IRD community overall. Within the Consortium, these data will be used to provide evidence-based support of which subset of diseases are appropriate targets for natural history studies and are useful for researchers determining which patient populations can best be served with the development of novel treatments. As the global footprint of the Consortium expands, future versions of the gene poll will continue to provide valuable insights regarding the genetic diversity of IRDs.

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