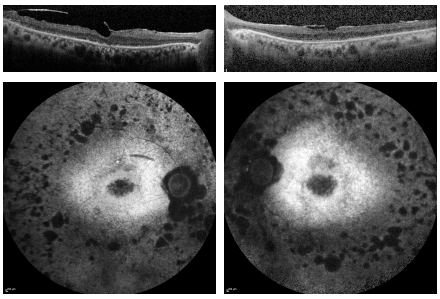
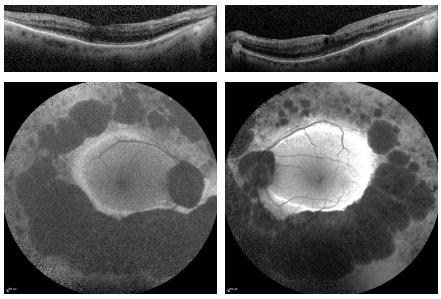
Supplementary Material

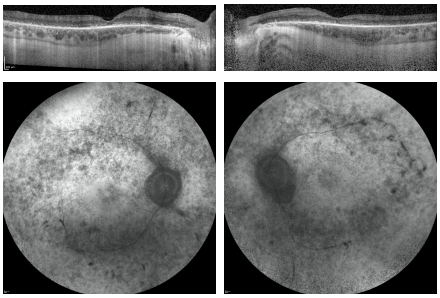
Figure S1 OCT and AF figures of patients D, G, H and K see Tables 1 and S3 for clinical and imaging information and Table S2 for details of electrophysiology.



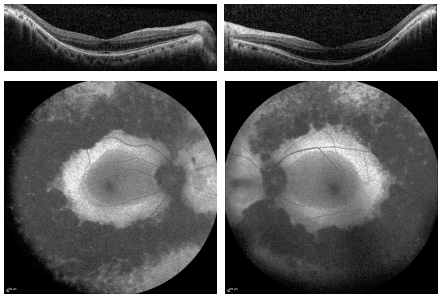
Patient D



Patient G



Patient H



Patient K

Supplementary Table 2. A summary of all the genetic studies in the literature relating to *EYS*

Author	Title	Number of *EYS* patients reported	Total number of *EYS* mutations reported	Number of novel *EYS* mutations reported	Phenotype information	Reference
Abd El-Aziz *et al.* 2008	*EYS*, encoding an ortholog of Drosophila spacemaker, is mutated in autosomal recessive retinitis pigmentosa	10	6	6	No	(1)
Abd El-Aziz *et al.* 2010	Identification of Novel Mutations in the Ortholog of Drosophila Eyes Shut Gene (*EYS*) Causing Autosomal Recessive Retinitis Pigmentosa	10	11	11	Yes	(2)
Arai *et al.* 2015	Retinitis Pigmentosa with *EYS* mutations is the most prevalent inherited retinal dystrophy in Japanese populations	82	62	32	No	(3)
Audo *et al.* 2010	*EYS* is a major gene for rod-cone dystrophies in France	29	39	37	Yes	(4)
Bandah-Rozenfeld *et al.* 2010	Novel Null Mutations in the *EYS* Gene Are a Frequent Cause of Autosomal Recessive Retinitis Pigmentosa in the Israeli Population	18	5	5	Yes	(5)
Beryozkin *et al.* 2014	Identification of Mutations Causing Inherited Retinal Degenerations in the Israeli and Palestinian Populations Using Homozygosity Mapping	1	1	1	Yes	(6)
Birtel *et al.* 2018	Next-generation sequencing identifies unexpected genotype-phenotype correlations in patients with retinitis pigmentosa.	10	17	7	No	(7)
Bonilha *et al.* 2015	Histopathological comparison of eyes from patients with autosomal recessive retinitis pigmentosa caused by novel *EYS* mutations	2	4	2	Yes	(8)
Burstedt *et al.* 2018	Phenotypic expression of *EYS* mutations in patients with autosomal recessive Retinitis Pigmentosa in Northern Sweden	13	5	3	No	(9)
Chen *et al.* 2015	Targeted next-generation sequencing reveals novel *EYS* mutations in Chinese families with autosomal recessive retinitis pigmentosa	7	4	2	Yes	(10)
Collin *et al.* 2008	Identification of a 2 Mb human ortholog of Drosophila eyes shut/spacemaker that is mutated in patients with retinitis pigmentosa	6	2	2	Yes	(11)
Dan *et al.* 2020	Application of targeted panel sequencing and whole exome sequencing for 76 Chinese families with retinitis pigmentosa	4	8	0	Yes	(12)
de Castro-Miro *et al.* 2016	Novel Candidate Genes and a Wide Spectrum of Structural and Point Mutations Responsible for Inherited Retinal Dystrophies Revealed by Exome Sequencing	1	2	1	No	(13)
Di *et al.* 2016	Whole-exome Sequencing Analysis Identifies Mutations in the *EYS* Gene in Retinitis Pigmentosa in the Indian Population	13	13	12	Yes	(14)

Eisenberger *et al.* 2013	Increasing the yield in targeted next-generation sequencing by implicating CNV analysis, non-coding exons and the overall variant load: the example of retinal dystrophies	5	8	7	No	(15)
Fuster-Garcia *et al.* 2019	Expanding the Genetic Landscape of Usher-like Phenotypes	1	2	0	Yes	(16)
Gattegna *et al.* 2019	Emerging Phenotypic Characteristics and Identification of Novel Mutations in Autosomal Recessive Retinitis Pigmentosa (ARRP) Associated with the *EYS* Gene	7	N/A	N/A	N/A	(17)
Ge *et al.* 2015	NGS-based Molecular diagnosis of 105 eyeGENE probands with Retinitis Pigmentosa.	5	11	6	No	(18)
Golovleva *et al.* 2016	Heterogeneity and complexity of *EYS* mutations in autosomal recessive retinitis pigmentosa in Northern Sweden	18	5	3	No	(19)
Gonzalez-del Pozo *et al.* 2011	Mutation screening of multiple genes in Spanish patients with AR RP by targeted re-sequencing	3	5	3	No	(20)
Gu *et al.* 2016	Targeted next-generation sequencing extends the phenotypic and mutational spectrums for *EYS* mutations	4	6	2	Yes	(21)
Haer-Wigman *et al.* 2017	Diagnostic exome sequencing in 266 Dutch patients with visual impairment	10	16	11	No	(22)
Hashmi *et al.* 2018	Whole exome sequencing identified a novel single base pair insertion mutation in the *EYS* gene in a six generation family with retinitis pigmentosa	12	1	1	Yes	(23)
Hosono *et al.* 2012	Two novel mutations in the *EYS* gene are possible major causes of autosomal recessive retinitis pigmentosa in the Japanese population	9	7	5	No	(24)
Huang *et al.* 2010	Identification of a novel homozygous nonsense mutation in *EYS* in a Chinese family with autosomal recessive retinitis pigmentosa	3	1	1	Yes	(25)
Huang *et al.* 2015	Genotype–phenotype correlation and mutation spectrum in a large cohort of patients with inherited retinal dystrophy revealed by next-generation sequencing	11	16	13	No	(26)
Huang *et al.* 2017	Mutation screening in genes known to be responsible for Retinitis Pigmentosa in 98 Small Han Chinese Families	2	3	2	No	(27)
Iwanami *et al.* 2012	High prevalence of mutations in the *EYS* gene in Japanese patients with AR RP	18	10	6	Yes	(28)
Iwanami *et al.* 2019	Five major sequence variants and copy number variants in the *EYS* gene account for one-third of Japanese patients with autosomal recessive and simplex retinitis pigmentosa	77	24	0	No	(29)
Jespersgaard *et al.* 2019	Molecular genetic analysis using targeted NGS analysis of 677 individuals with retinal dystrophy	29	22	7	No	(30)
Jiang *et al.* 2015	Comprehensive molecular diagnosis of 67 Chinese Usher syndrome probands: high rate of ethnicity specific mutations in Chinese USH patients	2	3	2	No	(31)
Jinda *et al.* 2014	Whole exome sequencing in Thai patients with retinitis pigmentosa reveals novel mutations in six genes	3	3	2	Yes	(32)
Kastner *et al.*	Exome Sequencing Reveals AGBL5 as Novel Candidate Gene and Additional Variants for	3	1	1	No	(33)

2015	Retinitis Pigmentosa in Five Turkish Families					
Katagiri *et al.* 2014	Whole exome analysis identifies frequent CNGA1 mutations in Japanese population with autosomal recessive retinitis pigmentosa	4	5	3	No	(34)
Khan *et al.* 2010	Missense mutations at homologous positions in the fourth and fifth laminin A G-like domains of eyes shut homolog cause autosomal recessive retinitis pigmentosa	6	2	2	Yes	(35)
Khateb *et al.* 2016	Identification of genomic deletions causing inherited retinal degenerations by coverage analysis of whole exome sequencing data	2	1	1	No	(36)
Kim *et al.* 2019	Genetic Mutation Profiles in Korean Patients with Inherited Retinal Diseases	4	7	3	No	(37)
Koyangi *et al.* 2019	Genetic characteristics of retinitis pigmentosa in 1204 Japanese patients	110	3	0	No	(38)
Littink *et al.* 2010	Mutations in the *EYS* gene account for approximately 5% of autosomal recessive retinitis pigmentosa and cause a fairly homogeneous phenotype	11	10	9	Yes	(39)
McGuigan *et al.* 2017	*EYS* mutations causing AR RP: changes of retinal structure and function with disease progression	15	25	9	Yes	(40)
Messchaert *et al.* 2018	*EYS* mutation update: *In silico* assessment of 271 reported and 26 novel variants in patients with retinitis pigmentosa	413	297	26	No	(41)
Miyata *et al.* 2017	Choroidal retinal atrophy of Bietti crystalline dystrophy patients with CYP4V2 mutations compared to retinitis pigmentosa patients with *EYS* mutations	10	8	0	Yes	(42)
Mucciolo *et al.* 2018	Fundus phenotype in retinitis pigmentosa associated with *EYS* mutations	10	13	9	Yes	(43)
Nishiguchi *et al.* 2013	Whole genome sequencing in patients with retinitis pigmentosa reveals pathogenic DNA structural changes and NEK2 as a new disease gene	1	2	2	No	(44)
Numa *et al.* 2019	Detailed characteristics of *EYS* variants in Japanese patients with retinitis pigmentosa	N/A	77	N/A	N/A	(45)
O'Sullivan *et al.* 2012	A paradigm shift in the delivery of services for diagnosis of inherited retinal disease	2	4	3	No	(46)
Oishi *et al.* 2014	Comprehensive molecular diagnosis of a large cohort of Japanese RP and Usher syndrome patients by next-generation sequencing	35	14	8	No	(47)
Perez-Carro *et al.* 2016	Panel-based NGS Reveals Novel Pathogenic Mutations in Autosomal Recessive Retinitis Pigmentosa	2	4	3	No	(48)
Pieras *et al.* 2011	Copy-number variations in *EYS*: a significant event in the appearance of arRP	9	12	6	No	(49)
Pierrache *et al.* 2019	Extending the spectrum of *EYS*-associated retinal disease to macular dystrophy	30	27	7	Yes	(50)
Pierrottet *et al.* 2014	Syndromic and non-syndromic forms of retinitis pigmentosa: a comprehensive Italian clinical and molecular study reveals new mutations	3	5	4	No	(51)

Riera *et al.* 2017	Whole exome sequencing using Ion Proton system enables reliable genetic diagnosis of inherited retinal dystrophies	2	4	3	No	(52)
Sengillo *et al.* 2018	A distinct phenotype of eyes shut homologue (*EYS*)-retinitis pigmentosa is associated with variants near the C-terminus	16	27	13	Yes	(53)
Sharon *et al.* 2020	A nationwide genetic analysis of inherited retinal diseases in Israel as assessed by the Israeli inherited retinal disease consortium	N/A	27	18	No	(54)
Sun *et al.* 2020	Genetic and clinical analysis in Chinese patients with retinitis pigmentosa caused by *EYS* mutations	4	3	3	Yes	(55)
Sun *et al.* 2020	Genetic and clinical findings of panel-based targeted exome sequencing in a northeast Chinese cohort with retinitis pigmentosa	2	4	2	Yes	(56)
Suto *et al.* 2014	Clinical phenotype in ten unrelated Japanese patients with mutations in the *EYS* gene	10	7	0	Yes	(57)
Tiwari *et al.* 2016	Next generation sequencing based identification of disease-associated mutations in Swiss patients with retinal dystrophies	1	2	2	No	(58)
Wang *et al.* 2014	Dependable and efficient clinical utility of target capture-based deep sequencing in molecular diagnosis of retinitis pigmentosa	4	9	7	No	(59)
Wang *et al.* 2018	Application of Whole Exome and Targeted Panel Sequencing in the Clinical Molecular Diagnosis of 319 Chinese Families with Inherited Retinal Dystrophy and Comparison Study	4	5	3	No	(60)
Weisschuh *et al.* 2016	Mutation Detection in Patients with Retinal Dystrophies Using Targeted Next Generation Sequencing	2	2	2	No	(61)
Wormser *et al.* 2018	Combined CNV, haplotyping and whole exome sequencing enable identification of two distinct novel *EYS* mutations causing RP in a single inbred tribe	9	2	2	Yes	(62)
Xiao *et al.* 2019	Whole exome sequencing reveals novel *EYS* mutations in Chinese patients with autosomal recessive retinitis pigmentosa	15	12	5	Yes	(63)
Xu *et al.* 2014	Mutations of 60 known causative genes in 157 families with retinitis pigmentosa based on exome sequencing	3	4	2	No	(64)
Yoon *et al.* 2015	The diagnostic application of targeted re-sequencing in Korean patients with retinitis pigmentosa	2	3	2	No	(65)
Zampaglione *et al.* 2020	Copy number variation contributes to 9% of pathogenicity in inherited retinal degenerations	29	43	11	No	(66)

Key | yellow highlight = EYS specific phenotype/genotype studies; no highlight = genotype only studies; N/A = conference abstract so data not available

References

1. Abd El-Aziz MM, Barragan I, O'Driscoll CA, Goodstadt L, Prigmore E, Borrego S, et al. EYS, encoding an ortholog of Drosophila spacemaker, is mutated in autosomal recessive retinitis pigmentosa. Nat Genet. 2008;40(11):1285-7.
2. Abd El-Aziz MM, O'Driscoll CA, Kaye RS, Barragan I, El-Ashry MF, Borrego S, et al. Identification of novel mutations in the ortholog of Drosophila eyes shut gene (EYS) causing autosomal recessive retinitis pigmentosa. Invest Ophthalmol Vis Sci. 2010;51(8):4266-72.
3. Arai Y, Maeda A, Hirami Y, Ishigami C, Kosugi S, Mandai M, et al. Retinitis Pigmentosa with EYS Mutations Is the Most Prevalent Inherited Retinal Dystrophy in Japanese Populations. J Ophthalmol. 2015;2015:819760.
4. Audo I, Sahel JA, Mohand-Said S, Lancelot ME, Antonio A, Moskova-Doumanova V, et al. EYS is a major gene for rod-cone dystrophies in France. Hum Mutat. 2010;31(5):E1406-35.
5. Bandah-Rozenfeld D, Littink KW, Ben-Yosef T, Strom TM, Chowers I, Collin RW, et al. Novel null mutations in the EYS gene are a frequent cause of autosomal recessive retinitis pigmentosa in the Israeli population. Invest Ophthalmol Vis Sci. 2010;51(9):4387-94.
6. Beryozkin A, Zelinger L, Bandah-Rozenfeld D, Shevach E, Harel A, Storm T, et al. Identification of mutations causing inherited retinal degenerations in the israeli and palestinian populations using homozygosity mapping. Invest Ophthalmol Vis Sci. 2014;55(2):1149-60.
7. Birtel J, Gliem M, Mangold E, Muller PL, Holz FG, Neuhaus C, et al. Next-generation sequencing identifies unexpected genotype-phenotype correlations in patients with retinitis pigmentosa. PLoS One. 2018;13(12):e0207958.
8. Bonilha VL, Rayborn ME, Bell BA, Marino MJ, Pauer GJ, Beight CD, et al. Histopathological comparison of eyes from patients with autosomal recessive retinitis pigmentosa caused by novel EYS mutations. Graefes Arch Clin Exp Ophthalmol. 2015;253(2):295-305.
9. Burstedt M, Jonsson F, Westein IM, Golovleva I. Phenotypic expression of EYS mutations in patients with autosomal recessive retinitis pigmentosa in northern Sweden. Invest Ophthalmol Vis Sci. 2018;59(9):19.
10. Chen X, Liu X, Sheng X, Gao X, Zhang X, Li Z, et al. Targeted next-generation sequencing reveals novel EYS mutations in Chinese families with autosomal recessive retinitis pigmentosa. Sci Rep. 2015;5:8927.
11. Collin RW, Littink KW, Klevering BJ, van den Born LI, Koenekoop RK, Zonneveld MN, et al. Identification of a 2 Mb human ortholog of Drosophila eyes shut/spacemaker that is mutated in patients with retinitis pigmentosa. Am J Hum Genet. 2008;83(5):594-603.
12. Dan H, Huang X, Xing Y, Shen Y. Application of targeted panel sequencing and whole exome sequencing for 76 Chinese families with retinitis pigmentosa. Mol Genet Genomic Med. 2020;8(3):e1131.
13. de Castro-Miro M, Tonda R, Escudero-Ferruz P, Andres R, Mayor-Lorenzo A, Castro J, et al. Novel Candidate Genes and a Wide Spectrum of Structural and Point Mutations Responsible for Inherited Retinal Dystrophies Revealed by Exome Sequencing. PLoS One. 2016;11(12):e0168966.
14. Di Y, Huang L, Sundaresan P, Li S, Kim R, Ballav Saikia B, et al. Whole-exome Sequencing Analysis Identifies Mutations in the EYS Gene in Retinitis Pigmentosa in the Indian Population. Sci Rep. 2016;6:19432.
15. Eisenberger T, Neuhaus C, Khan AO, Decker C, Preising MN, Friedburg C, et al. Increasing the yield in targeted next-generation sequencing by implicating CNV analysis, non-coding exons and the overall variant load: the example of retinal dystrophies. PLoS One. 2013;8(11):e78496.
16. Fuster-Garcia C, Garcia-Garcia G, Jaijo T, Blanco-Kelly F, Tian L, Hakonarson H, et al. Expanding the Genetic Landscape of Usher-Like Phenotypes. Invest Ophthalmol Vis Sci. 2019;60(14):4701-10.
17. Gattegna R, Bleicher I, Iannaccone A. Emerging Phenotypic Characteristics and Identification of Novel Mutations in Autosomal Recessive Retinitis Pigmentosa (ARRP) Associated with the EYS Gene. Invest Ophthalmol Vis Sci. 2019;60(9):4508.
18. Ge Z, Bowles K, Goetz K, Scholl HP, Wang F, Wang X, et al. NGS-based Molecular diagnosis of 105 eyeGENE((R)) probands with Retinitis Pigmentosa. Sci Rep. 2015;5:18287.

19. Golovleva I, Jonsson F, Burstedt M. Heterogeneity and complexity of EYS mutations in autosomal recessive retinitis pigmentosa in northern Sweden. Invest Ophthalmol Vis Sci. 2016;57(9):3136.
20. Gonzalez-del Pozo M, Borrego S, Barragan I, Pieras JI, Santoyo J, Matamala N, et al. Mutation screening of multiple genes in Spanish patients with autosomal recessive retinitis pigmentosa by targeted resequencing. PLoS One. 2011;6(12):e27894.
21. Gu S, Tian Y, Chen X, Zhao C. Targeted next-generation sequencing extends the phenotypic and mutational spectrums for EYS mutations. Mol Vis. 2016;22:646-57.
22. Haer-Wigman L, van Zelst-Stams WA, Pfundt R, van den Born LI, Klaver CC, Verheij JB, et al. Diagnostic exome sequencing in 266 Dutch patients with visual impairment. Eur J Hum Genet. 2017;25(5):591-9.
23. Hashmi JA, Albarry MA, Almatrafi AM, Albalawi AM, Mahmood A, Basit S. Whole exome sequencing identified a novel single base pair insertion mutation in the EYS gene in a six generation family with retinitis pigmentosa. Congenit Anom (Kyoto). 2018;58(1):10-5.
24. Hosono K, Ishigami C, Takahashi M, Park DH, Hirami Y, Nakanishi H, et al. Two novel mutations in the EYS gene are possible major causes of autosomal recessive retinitis pigmentosa in the Japanese population. PLoS One. 2012;7(2):e31036.
25. Huang Y, Zhang J, Li C, Yang G, Liu M, Wang QK, et al. Identification of a novel homozygous nonsense mutation in EYS in a Chinese family with autosomal recessive retinitis pigmentosa. BMC Med Genet. 2010;11:121.
26. Huang XF, Huang F, Wu KC, Wu J, Chen J, Pang CP, et al. Genotype-phenotype correlation and mutation spectrum in a large cohort of patients with inherited retinal dystrophy revealed by next-generation sequencing. Genet Med. 2015;17(4):271-8.
27. Huang L, Zhang Q, Huang X, Qu C, Ma S, Mao Y, et al. Mutation screening in genes known to be responsible for Retinitis Pigmentosa in 98 Small Han Chinese Families. Sci Rep. 2017;7(1):1948.
28. Iwanami M, Oshikawa M, Nishida T, Nakadomari S, Kato S. High prevalence of mutations in the EYS gene in Japanese patients with autosomal recessive retinitis pigmentosa. Invest Ophthalmol Vis Sci. 2012;53(2):1033-40.
29. Iwanami M, Oishi A, Ogino K, Seko Y, Nishida-Shimizu T, Yoshimura N, et al. Five major sequence variants and copy number variants in the EYS gene account for one-third of Japanese patients with autosomal recessive and simplex retinitis pigmentosa. Mol Vis. 2019;25:766-79.
30. Jespersgaard C, Fang M, Bertelsen M, Dang X, Jensen H, Chen Y, et al. Molecular genetic analysis using targeted NGS analysis of 677 individuals with retinal dystrophy. Sci Rep. 2019;9(1):1219.
31. Jiang L, Liang X, Li Y, Wang J, Zaneveld JE, Wang H, et al. Comprehensive molecular diagnosis of 67 Chinese Usher syndrome probands: high rate of ethnicity specific mutations in Chinese USH patients. Orphanet J Rare Dis. 2015;10:110.
32. Jinda W, Taylor TD, Suzuki Y, Thongnoppakhun W, Limwongse C, Lertrit P, et al. Whole exome sequencing in Thai patients with retinitis pigmentosa reveals novel mutations in six genes. Invest Ophthalmol Vis Sci. 2014;55(4):2259-68.
33. Kastner S, Thiemann IJ, Dekomien G, Petrasch-Parwez E, Schreiber S, Akkad DA, et al. Exome Sequencing Reveals AGBL5 as Novel Candidate Gene and Additional Variants for Retinitis Pigmentosa in Five Turkish Families. Invest Ophthalmol Vis Sci. 2015;56(13):8045-53.
34. Katagiri S, Akahori M, Sergeev Y, Yoshitake K, Ikeo K, Furuno M, et al. Whole exome analysis identifies frequent CNGA1 mutations in Japanese population with autosomal recessive retinitis pigmentosa. PLoS One. 2014;9(9):e108721.
35. Khan MI, Collin RW, Arimadyo K, Micheal S, Azam M, Qureshi N, et al. Missense mutations at homologous positions in the fourth and fifth laminin A G-like domains of eyes shut homolog cause autosomal recessive retinitis pigmentosa. Mol Vis. 2010;16:2753-9.
36. Khateb S, Hanany M, Khalaileh A, Beryozkin A, Meyer S, Abu-Diab A, et al. Identification of genomic deletions causing inherited retinal degenerations by coverage analysis of whole exome sequencing data. J Med Genet. 2016;53(9):600-7.
37. Kim MS, Joo K, Seong MW, Kim MJ, Park KH, Park SS, et al. Genetic Mutation Profiles in Korean Patients with Inherited Retinal Diseases. J Korean Med Sci. 2019;34(21):e161.
38. Koyanagi Y, Akiyama M, Nishiguchi KM, Momozawa Y, Kamatani Y, Takata S, et al. Genetic characteristics of retinitis pigmentosa in 1204 Japanese patients. J Med Genet. 2019;56(10):662-70.

39. Littink KW, van den Born LI, Koenekoop RK, Collin RW, Zonneveld MN, Blokland EA, et al. Mutations in the EYS gene account for approximately 5% of autosomal recessive retinitis pigmentosa and cause a fairly homogeneous phenotype. Ophthalmology. 2010;117(10):2026-33, 33 e1-7.
40. McGuigan DB, Heon E, Cideciyan AV, Ratnapriya R, Lu M, Sumaroka A, et al. EYS Mutations Causing Autosomal Recessive Retinitis Pigmentosa: Changes of Retinal Structure and Function with Disease Progression. Genes (Basel). 2017;8(7).
41. Messchaert M, Haer-Wigman L, Khan MI, Cremers FPM, Collin RWJ. EYS mutation update: In silico assessment of 271 reported and 26 novel variants in patients with retinitis pigmentosa. Hum Mutat. 2018;39(2):177-86.
42. Miyata M, Hata M, Ooto S, Ogino K, Gotoh N, Morooka S, et al. Choroidal and Retinal Atrophy of Bietti Crystalline Dystrophy Patients with Cyp4v2 Mutations Compared to Retinitis Pigmentosa Patients with Eys Mutations. Retina. 2017;37(6):1193-202.
43. Mucciolo DP, Sodi A, Passerini I, Murro V, Cipollini F, Borg I, et al. Fundus phenotype in retinitis pigmentosa associated with EYS mutations. Ophthalmic Genet. 2018;39(5):589-602.
44. Nishiguchi KM, Tearle RG, Liu YP, Oh EC, Miyake N, Benaglio P, et al. Whole genome sequencing in patients with retinitis pigmentosa reveals pathogenic DNA structural changes and NEK2 as a new disease gene. Proc Natl Acad Sci U S A. 2013;110(40):16139-44.
45. Numa S, Oishi A, Oishi M, Hasegawa T, Ishihara K, Miyata M, et al. Detailed characteristics of EYS variants in Japanese patients with retinitis pigmentosa. Invest Ophthalmol Vis Sci. 2019;60(9):4522.
46. O'Sullivan J, Mullaney BG, Bhaskar SS, Dickerson JE, Hall G, O'Grady A, et al. A paradigm shift in the delivery of services for diagnosis of inherited retinal disease. J Med Genet. 2012;49(5):322-6.
47. Oishi M, Oishi A, Gotoh N, Ogino K, Higasa K, Iida K, et al. Comprehensive molecular diagnosis of a large cohort of Japanese retinitis pigmentosa and Usher syndrome patients by next-generation sequencing. Invest Ophthalmol Vis Sci. 2014;55(11):7369-75.
48. Perez-Carro R, Corton M, Sanchez-Navarro I, Zurita O, Sanchez-Bolivar N, Sanchez-Alcudia R, et al. Panel-based NGS Reveals Novel Pathogenic Mutations in Autosomal Recessive Retinitis Pigmentosa. Sci Rep. 2016;6:19531.
49. Pieras JI, Barragan I, Borrego S, Audo I, Gonzalez-Del Pozo M, Bernal S, et al. Copy-number variations in EYS: a significant event in the appearance of arRP. Invest Ophthalmol Vis Sci. 2011;52(8):5625-31.
50. Pierrache LHM, Messchaert M, Thiadens A, Haer-Wigman L, de Jong-Hesse Y, van Zelst-Stams WAG, et al. Extending the Spectrum of EYS-Associated Retinal Disease to Macular Dystrophy. Invest Ophthalmol Vis Sci. 2019;60(6):2049-63.
51. Pierrottet CO, Zuntini M, Digiuni M, Bazzanella I, Ferri P, Paderni R, et al. Syndromic and non-syndromic forms of retinitis pigmentosa: a comprehensive Italian clinical and molecular study reveals new mutations. Genet Mol Res. 2014;13(4):8815-33.
52. Riera M, Navarro R, Ruiz-Nogales S, Mendez P, Bures-Jelstrup A, Corcostegui B, et al. Whole exome sequencing using Ion Proton system enables reliable genetic diagnosis of inherited retinal dystrophies. Sci Rep. 2017;7:42078.
53. Sengillo JD, Lee W, Nagasaki T, Schuerch K, Yannuzzi LA, Freund KB, et al. A Distinct Phenotype of Eyes Shut Homolog (EYS)-Retinitis Pigmentosa Is Associated With Variants Near the C-Terminus. Am J Ophthalmol. 2018;190:99-112.
54. Sharon D, Ben-Yosef T, Goldenberg-Cohen N, Pras E, Gradstein L, Soudry S, et al. A nationwide genetic analysis of inherited retinal diseases in Israel as assessed by the Israeli inherited retinal disease consortium (IIRDC). Hum Mutat. 2020;41(1):140-9.
55. Sun Y, Li JK, He W, Wang ZS, Bai JY, Xu L, et al. Genetic and clinical analysis in Chinese patients with retinitis pigmentosa caused by EYS mutations. Mol Genet Genomic Med. 2020;8(3):e1117.
56. Sun Y, Li W, Li JK, Wang ZS, Bai JY, Xu L, et al. Genetic and clinical findings of panel-based targeted exome sequencing in a northeast Chinese cohort with retinitis pigmentosa. Mol Genet Genomic Med. 2020:e1184.
57. Suto K, Hosono K, Takahashi M, Hirami Y, Arai Y, Nagase Y, et al. Clinical phenotype in ten unrelated Japanese patients with mutations in the EYS gene. Ophthalmic Genet. 2014;35(1):25-34.

58. Tiwari A, Bahr A, Bahr L, Fleischhauer J, Zinkernagel MS, Winkler N, et al. Next generation sequencing based identification of disease-associated mutations in Swiss patients with retinal dystrophies. Sci Rep. 2016;6:28755.
59. Wang J, Zhang VW, Feng Y, Tian X, Li FY, Truong C, et al. Dependable and efficient clinical utility of target capture-based deep sequencing in molecular diagnosis of retinitis pigmentosa. Invest Ophthalmol Vis Sci. 2014;55(10):6213-23.
60. Wang L, Zhang J, Chen N, Wang L, Zhang F, Ma Z, et al. Application of Whole Exome and Targeted Panel Sequencing in the Clinical Molecular Diagnosis of 319 Chinese Families with Inherited Retinal Dystrophy and Comparison Study. Genes (Basel). 2018;9(7).
61. Weisschuh N, Mayer AK, Strom TM, Kohl S, Glockle N, Schubach M, et al. Mutation Detection in Patients with Retinal Dystrophies Using Targeted Next Generation Sequencing. PLoS One. 2016;11(1):e0145951.
62. Wormser O, Gradstein L, Kadar E, Yogev Y, Perez Y, Mashkit E, et al. Combined CNV, haplotyping and whole exome sequencing enable identification of two distinct novel EYS mutations causing RP in a single inbred tribe. Am J Med Genet A. 2018;176(12):2695-703.
63. Xiao X, Cao Y, Chen S, Chen M, Mai X, Zheng Y, et al. Whole exome sequencing reveals novel EYS mutations in Chinese patients with autosomal recessive retinitis pigmentosa. Mol Vis. 2019;25:35-46.
64. Xu Y, Guan L, Shen T, Zhang J, Xiao X, Jiang H, et al. Mutations of 60 known causative genes in 157 families with retinitis pigmentosa based on exome sequencing. Hum Genet. 2014;133(10):1255-71.
65. Yoon CK, Kim NK, Joung JG, Shin JY, Park JH, Eum HH, et al. The diagnostic application of targeted re-sequencing in Korean patients with retinitis pigmentosa. BMC Genomics. 2015;16:515.
66. Zampaglione E, Kinde B, Place EM, Navarro-Gomez D, Maher M, Jamshidi F, et al. Copy-number variation contributes 9% of pathogenicity in the inherited retinal degenerations. Genet Med. 2020.

Table S2 showing the electrophysiology details for patients B, F I and L with abnormal values highlighted in red.

Left Eye						
Patient	0.01 Dark Adapted Rod ERG			3.0 Light Adapted Cone ERG		
	Latency (ms)		a-b amplitude (μV)	Latency (ms)		a-b amplitude (μV)
	a	b		a	b	
B	83.2	106.4	15.2	15.2	36.4	29.1
F	42.0	95.0	131.0	13.0	32.0	41.0
I	34.0	81.0	59.0	14.0	39.0	25.0
L	53.5	133.5	11.4	23.5	35.0	19.4
Normal values	39.1±8.3	98.8±19.6	234.2±143.5	16.9±2.1	29.8±3.9	119.5±43.4
Right Eye						
Patient	0.01 Dark Adapted Rod ERG			3.0 Light Adapted Cone ERG		
	Latency (ms)		a-b amplitude (μV)	Latency (ms)		a-b amplitude (μV)
	a	b		a	b	
B	80.8	111.2	36.0	15.6	35.6	21.2
F	39.0	97.0	142.0	16.0	30.0	46.0
I	40.0	91.0	50.0	14.0	34.0	46.0
L	53.4	133.5	81.5	16.5	38.5	18.1
Normal values	39.1±8.3	98.8±19.6	234.2±143.5	16.9±2.1	29.8±3.9	119.5±43.4

Patient	Autofluorescence	CMT OS	CMT OD	OCT
A	Well demarcated dense loss of signal centrally, less dense atrophy external to arcades, consistent with atrophy; increased AF signal within maculae	368	267	Loss of ellipsoid zone peripherally, macular sparing, sparing of foveal contour; thin retinas
B	Eccentric annular ring of increased AF signal, central sparing, patchy loss of AF signal corresponding to atrophic change in area of spicules	238	230	Central sparing of ellipsoid zone, peripheral atrophy; thin retina
C	Annular ring R>L, central sparing patchy loss of AF signal corresponding to atrophic change in area of spicules	214	182	Loss of ellipsoid zone peripherally
D	Well demarcated dense loss of signal centrally, less patchy atrophy external to arcades, consistent with atrophy; increased AF signal within maculae	246	271	Epiretinal membranes, retinal thinning, loss of ellipsoid zone, hypereflective dots at the interdigitation zone.
E	Inferior sector atrophic change with band of increased AF at edge of atrophic change encroaching and including inferior arcades.	329	336	Central thickness preserved.
F	Increased band of AF extending through inferior and up to superior arcades with reduced AF signal within and extending through inferior atrophic area in sectoral distribution	236	168	Partial thickness macular hole OS with epiretinal membrane, disruption of ILM OD; loss of ellipsoid zone external to fovea
G	Annular ring of increased AF surrounding arcades with large coalescing areas of decreased signal consistent with atrophic patches located circumferential to the arcades in mid retina	275	248	Relative central sparing, but marked ellipsoid zone discontinuity, especially peripherally, cystic spaces bilaterally
H	Patchy loss of signal in posterior pole extending through mid periphery mainly located at arcades with decreased signal located parafoveally consistent with atrophy around the fovea.	164	204	Loss of ellipsoid zone and gross thinning of the retina. Hyperreflective dots at the interdigitation zone
I	Images not interpretable	214	225	Poor quality images (not shown) loss of ellipsoid zone external to fovea Good foveal contour, central sparing of ellipsoid zone, peripheral atrophy
J	Marked atrophy, central island of increased AF signal	208	238	Loss of ellipsoid zone at temporal to macula, some hyper reflective dots at the interdigitation zone
K	Band of increased AF surrounding macula with coalescing patches of decreased signal consistent with atrophy in concentric ring external to arcades in mid periphery with increased ring of AF nasal to the disc	228	223	Loss of ellipsoid zone continuity temporal to maculas and adjacent to discs
L	Widespread patchy reduction in AF signal with increased signal in far periphery temporally.	329	336	Central sparing, marked peripheral atrophy

Table S3 Details of autofluorescence and optical coherence tomography imaging