


CLINICAL REPORT

Novel hemizygous single-nucleotide duplication in *RPGR* in a patient with retinal dystrophy and sensorineural hearing loss

Ryan J. German^{1,2}  | Blake Vuocolo^{1,2} | Liesbeth Vossaert^{1,3} | Nichole Owen^{1,3} | Richard A. Lewis^{1,4,5} | Lisa Saba⁶ | The Texome Project | Michael F. Wangler^{1,2,7} | Sandesh Nagamani^{1,4,7}

¹Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas, USA

²Jan and Dan Duncan Neurological Research Institute, Texas Children's Hospital, Houston, Texas, USA

³Baylor Genetics Laboratories, Houston, Texas, USA

⁴Department of Medicine, Baylor College of Medicine, Houston, Texas, USA

⁵Department of Ophthalmology, Baylor College of Medicine, Houston, Texas, USA

⁶Department of Pathology, Texas Children's Hospital, Houston, Texas, USA

⁷Texas Children's Hospital, Houston, Texas, USA

Correspondence

Michael F. Wangler, Department of Molecular and Human Genetics, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, USA.
Email: michael.wangler@bcm.edu

Funding information

Jan and Dan Duncan Neurological Research Institute of Texas Children's Hospital; Eunice Kennedy Shriver National Institute of Child Health and Human Development, Grant/Award Number: P50HD103555; National Human Genome Research Institute, Grant/Award Number: R01HG011795

Abstract

Background: The *RPGR* gene has been associated with X-linked cone-rod dystrophy. This report describes a variant in *RPGR* detected with exome sequencing (ES). Genes like *RPGR* have not always been included in panel-based testing and thus genome-wide tests such as ES may be required for accurate diagnosis.

Methods: The Texome Project is studying the impact of ES in medically underserved patients who are in need of genomic testing to guide diagnosis and medical management. The hypothesis is that ES could uncover diagnoses not made by standard medical care.

Results: A 58-year-old male presented with retinitis pigmentosa, sensorineural hearing loss, and a family history of retinal diseases. A previous targeted gene panel for retinal disorders had not identified a molecular cause. ES through the Texome Project identified a novel, hemizygous variant in *RPGR* (NM_000328.3: c.1302dup, p.L435Sfs*18) that explained the ocular phenotype.

Conclusions: Continued genetics evaluation can help to end diagnostic odysseys of patients. Careful consideration of genes represented when utilizing gene panels is crucial to ensure an accurate diagnosis. Medically underserved populations are less likely to receive comprehensive genetic testing in their diagnostic

Texome Project Members listed in [Table S2](#).

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial License](#), which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2024 The Authors. *Molecular Genetics & Genomic Medicine* published by Wiley Periodicals LLC.

workup. Our report is an example of the medical impact of genomic medicine implementation.

KEYWORDS

exome sequencing, retinal dystrophy, retinitis pigmentosa, RPGR

1 | INTRODUCTION

Recent studies have shown that an increasing proportion of blindness among younger and working-age adults is caused by genetic disorders of the eye including inherited retinal dystrophy, which has an estimated prevalence between 0.06% and 0.2% (Hanany et al., 2020; Heath Jeffery et al., 2021). Inherited retinal dystrophy comprises a group of genetically heterogeneous disorders and to date, pathogenic variants in over 700 genes have been discovered as causal for these disorders. *Retinitis pigmentosa GTPase regulator (RPGR)*, located on Xp11.4, is associated with a wide phenotypic spectrum of retinal diseases, including retinitis pigmentosa 3 (MIM300029), X-linked retinitis pigmentosa and sinorespiratory infections with or without deafness (MIM300455), X-linked cone-rod dystrophy (MIM304020), and X-linked atrophic macular degeneration (MIM300834) (Ayyagari et al., 2002; Demirci et al., 2002; Roepman et al., 1996; Zito et al., 2003). Pathogenic variants in *RPGR* have been reported to cause nearly two-thirds of all X-linked retinitis pigmentosa (Khanna et al., 2005; Mihailovic et al., 2022; Vervoort et al., 2000). Individuals with *RPGR*-related X-linked retinitis pigmentosa (XLRP) have an aggressive form of the disease, characterized by night blindness in the first or second decades of life, followed by progressive loss of visual acuity and legal blindness by the third or fourth decades of life (Di Iorio et al., 2020; Georgiou et al., 2021; Nguyen et al., 2020; Sandberg et al., 2007). Individuals with *RPGR*-related retinal diseases can also manifest extraocular phenotypes, including hearing loss, chronic otitis media, sinusitis, bronchitis, and bronchiectasis (Georgiou et al., 2021; Zito et al., 2003). Due to X-linked inheritance, most affected individuals are hemizygous males. However, heterozygous female carriers can also have ocular findings which can range from minimal visual impairment to severe retinitis pigmentosa (RP), sometimes with extraocular findings, particularly sinusitis, otitis media, and hearing loss (Georgiou et al., 2021; Tuupanen et al., 2022; Zito et al., 2003).

As there is significant clinical variability and phenotypic overlap between inherited retinal disorders, an accurate diagnosis is often dependent on molecular genetic testing; gene panel-based testing has become a standard approach in many clinics. This creates a disparity for

medically underserved and under-resourced groups of the population who do not have access to genomic medicine. Such disparity occurs due to many factors, including decreased ability to navigate the healthcare system due to impaired vision, financial difficulty resulting from RP, and lack of access to genetic services. Additionally, long wait times to obtain a genetics referral and delays associated with getting appropriate comprehensive testing are barriers to having timely access to therapeutic approaches such as cell therapy and gene therapy (Cross et al., 2022).

Access to comprehensive genetic testing such as exome sequencing (ES) and whole genome sequencing (WGS) is crucial to find answers for patients and families with undiagnosed inherited retinal disorders. For many individuals such genome-wide genetic testing has been inaccessible because of a lack of resources in their communities, lack of insurance coverage, and inability to travel to medical providers with genetics expertise (Chou et al., 2021; National Academies of Sciences, 2018; Reuter et al., 2019; Schoch et al., 2021). XLRP confers a significant emotional, social, physical, and economic burden on patients because of its progressive nature that interferes with one's ability to independently perform activities of daily living (Chaumet-Riffaud et al., 2017). Several studies have shown that RP severely impacts quality of life as the condition presents barriers to traditional employment, hobbies, and family life. Furthermore, caregivers are also impacted by secondary exclusion from activities in which their loved one(s) cannot participate and by barriers to employment because of their caregiving role (Chivers et al., 2021; Watanabe et al., 2023). However, with support from appropriate social, healthcare, and educational services, some of these burdens can be decreased (Bertelsen et al., 2015). The Texome Project is a genomic implementation program focused on providing ES from a clinical genetics diagnostic laboratory to investigate the molecular cause(s) of undiagnosed diseases in populations that have not historically had access to genomic medicine due to a variety of barriers. The Texome Project includes the opportunity for reanalysis of genetic data and model organism study of candidate variants if ES is nondiagnostic. Participants are also engaged in a 2-year longitudinal follow-up of the perceptions, utility, and barriers they associate with genomic medicine. Here, we report on a molecular genetic diagnosis with ES in an individual with RP,

in whom a molecular cause had not been identified after standard, panel-based testing.

2 | MATERIALS AND METHODS

2.1 | Ethical compliance

Informed consent was obtained from the participant under the Baylor College of Medicine Institutional Review Board Protocol H-49277 prior to participation in the Texome Project, a National Human Genome Research Institute (NHGRI) and private philanthropic-funded study that explores the diagnostic value of WES on the care of medically underserved children and adults with genetic diseases. The study enrolls individuals with phenotype compatible with a Mendelian genetic disease and individuals with complex clinical presentations where one diagnosis is not likely to explain the phenotype. Medical history was obtained by a review of the medical records.

ES was performed on DNA isolated from a buccal swab at Baylor Genetics Laboratory, a tertiary that is certified by the College of American Pathologists and is compliant with the Clinical Laboratory Improvement Amendments. The isolated DNA was indexed into separate libraries using the KAPA Hyper Prep Kit. Illumina paired-end massively parallel sequencing with 100bp insert size was performed. The sequencing had a mean read depth of 159× with 98.9% of exons having at least 20× coverage. Data were aligned to the human reference genome build GRCh37 (Hg19). Data analysis and filtration were performed using the Illumina Dragen BioIT platform, Illumina Dragen haplotype-based variant caller and Illumina Dragen genome-wide depth-based CNV caller. Variant interpretation was performed using EMEDGENE software (Illumina), and curation was performed in accordance with the ACMG guidelines (Richards et al., 2015).

3 | RESULTS

The participant was accepted into the Texome Project based on objective abnormal findings that indicated a genetic etiology, unique clinical presentation, multiple organ system involvement, and family history of retinal disease.

3.1 | Clinical presentation

A 58-year-old male with cone-rod dystrophy and sensorineural hearing loss was referred to the Texome Project. This individual was diagnosed with retinitis pigmentosa

at the age of 6 years as he had developed night blindness and had clinical findings suggestive of progressive bilateral retinal dystrophy. His vision had progressively deteriorated and at the time of evaluation at the genetics clinic, at the age of 57 years, he was legally blind. At 55 years of age, he also developed vertigo and hearing loss which had progressed rapidly over the preceding two years. Additionally, throughout his life, he exhibited right-sided hemihypertrophy and macrocephaly. The family history was significant for a history of RP in the mother (age of onset 40 years), maternal uncle (age of onset unknown), and a female cousin through this maternal uncle (age of onset unknown). The sister of the proband had a diagnosis of “macular degeneration” (Figure 1). Physical examination at 57 years of age revealed mild hemihypertrophy with the right arm and forearms measuring 4 cm larger than the left. Mild hemihypertrophy was also noted in the right thigh and leg regions. An ophthalmology examination showed light perception in the right eye and no light perception in the left eye. The fundi exhibited vitreous syneresis, scattered pigmented cells, and features of classic end-stage retinitis pigmentosa (Figure 2).

Based on the phenotype, a commercially available inherited retinal disorders panel was ordered. This panel, which interrogated sequence variants and copy number variants in 293 genes known to cause retinal dystrophies (Table S1), did not identify a molecular diagnosis. We were unable to perform a genome-wide genetic test because of the complex logistical and financial challenges surrounding access to genomic medicine in the United States. Thus, the individual was enrolled in the Texome Project (Figure 3).

3.2 | Genetic diagnosis

ES identified a single-nucleotide duplication in *RPGR* (c.1302dup, p.L435Sfs*18) (ClinVar ID:1707409). This variant causes a frameshift in exon 11, leading to a premature termination codon which is predicted to result in nonsense-mediated decay. This novel change is absent from GnomAD and has not been described previously in Clinvar. This result provides a molecular cause for the retinal dystrophy and may explain the hearing loss in our patient as no other genetic etiology was found. The exome sequencing did not identify any variants in known genes associated with hearing loss genes other than *RPGR*. Due to the later onset hearing loss for our patient, age may also be a factor in this case. However, we were not able to identify a molecular cause for the hemihypertrophy and macrocephaly observed in the proband. The *RPGR* gene was not included on the commercially available panel by the laboratory because of technical challenges associated with

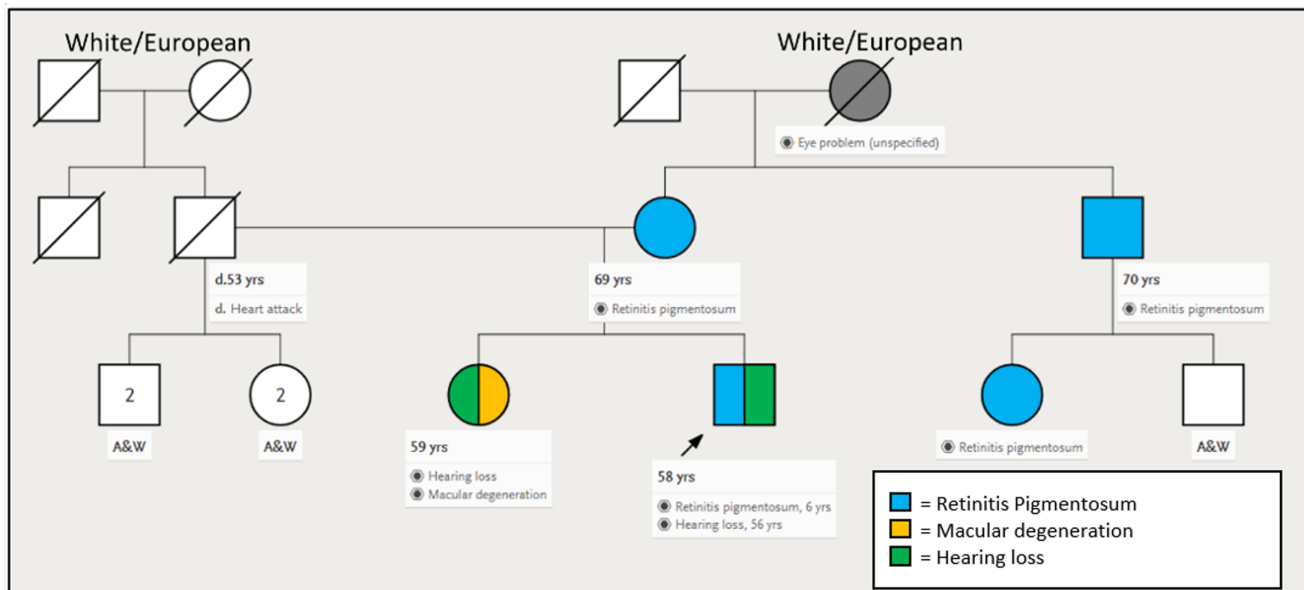


FIGURE 1 Pedigree indicating a substantial family history of retinitis pigmentosa, macular degeneration, and other ocular issues in both males and females. We were only able to perform proband WES as other family members were not available for testing. Our historian for the pedigree was the proband. A&W, alive and well; d., deceased; yrs, years; blue, retinitis pigmentosa; green, hearing loss; yellow, macular degeneration.



FIGURE 2 Images taken with a Zeiss FF450plus fundus camera show classic end-stage retinitis pigmentosa bilaterally. The camera settings were not altered between imaging of each eye. (a) Right eye, (b) left eye.

sequencing the repetitive glutamic acid and glycine-rich areas involved in the open reading frame of *RPGR*_{ORF15} (Maggi et al., 2020). As a result, the *RPGR*-related RP diagnosis was missed with panel testing.

4 | DISCUSSION

The *RPGR* protein plays an important role in the function of photoreceptors connecting cilia that are responsible for trafficking proteins to the outer segments of photoreceptors in the retina. Furthermore, *RPGR* has kinociliary functions in nonocular tissue, including the testis, kidneys, brain, lungs, and pancreas (Georgiou et al., 2021; Ghosh et al., 2010; Moreno-Leon et al., 2021; Zito et al., 2003).

There are two well-described isoforms of *RPGR*. The first isoform has 19 exons encoding 815 amino acids and is constitutively expressed, while the second shares the first 14 exons and then has an open reading frame at exon 15 (*RPGR*_{ORF15}) that includes part of intron 15 as the last exon. *RPGR*_{ORF15} is expressed exclusively in the connecting cilium of photoreceptors of the retina (Di Iorio et al., 2020; Georgiou et al., 2021; Khanna et al., 2005; Moreno-Leon et al., 2021; Vervoort et al., 2000). The terminal exon 15 is a hotspot for mutations due to glutamate-glycine repeats and accounts for up to 80% of disease-causing variants (Di Iorio et al., 2020; Nguyen et al., 2020). The proband's variant falls in the second quartile of exon 11. While there are various reports on whether the phenotypes of individuals with mutations in exons 1–14 are more severe than those

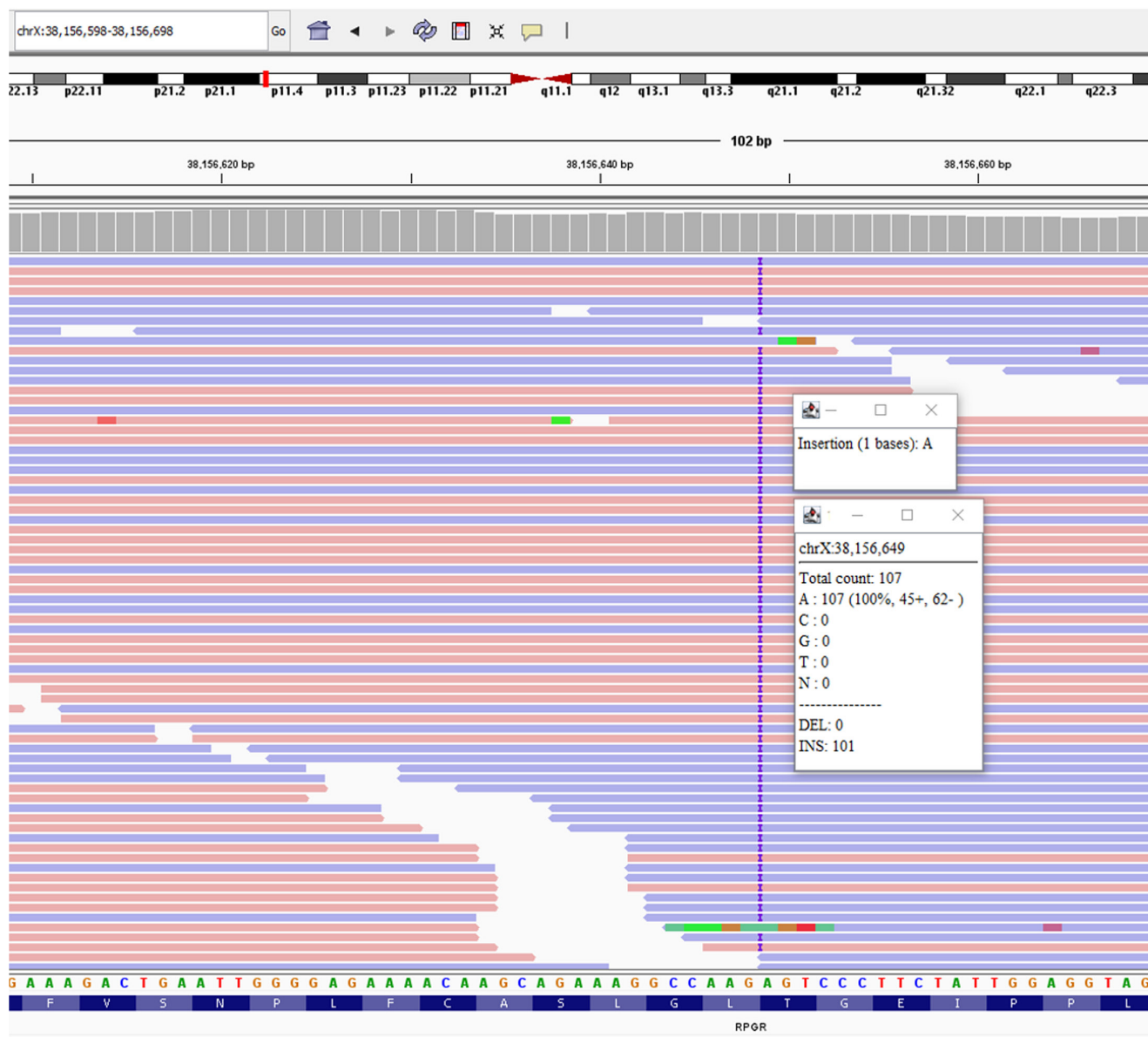


FIGURE 3 Next generation sequencing data exhibiting the single-nucleotide duplication on all 107 reads at NM_000328.3: c.1302dup; [hg19]chrX:38156648G>GA.

with mutations in ORF15, the extraocular findings such as in our patient have been described only in variants in exons 1–14 (Di Iorio et al., 2020; Sandberg et al., 2007; Talib et al., 2019; Zou et al., 2020).

When utilizing targeted panels in patients with rare diseases, cases with etiologies related to lesser-known genes or recently established gene-disease relationships can be missed since the process of adding genes to panels can be lengthy. In the case of *RPGR*, almost 10 years passed from the time a definitive disease relationship was outlined by Branham et al. to the time that *RPGR* was added to many retinal disease gene panels. Comprehensive genetic testing using ES or WGS can address this concern with complete coverage of the exome or genome, respectively, enabling evidence to be built from candidate genes. However, for

individuals from underserved populations, access to panel testing may be significantly higher than access to ES or WGS because of current insurance payor coverage guidelines for public insurance. Particularly in scenarios where there is discordance from the expected inheritance pattern, as seen in female carriers of X-linked *RPGR* who can have similar presentations to affected hemizygous males, the diagnostic process can prove difficult because of variable expressivity in both males and females (Georgiou et al., 2021; Nanda et al., 2018; Tuupainen et al., 2022). Thus, the implementation of genetics services and comprehensive genetic testing in underserved populations, such as through the Texome Project, is key to transitioning to a more equitable era of genomic medicine that serves to guide care and management of disease in diverse groups.

Genomic medicine has been an instrumental tool in diagnosing individuals with rare diseases and limiting the diagnostic odyssey phenomenon (El Naofal et al., 2023; Wiener et al., 2023). Genetic testing has proved to be a cost-effective way to diagnose conditions and direct medical resources toward appropriate therapies, surveillance, or treatment, though many barriers and limitations remain implementation of such testing (Muth et al., 2019; O'Brien et al., 2021; Serrano et al., 2023). The COVID-19 pandemic both exposed these access disparities and eased some barriers by increasing the uptake of telemedicine in genetics clinics, willingness to share genetic information, and to undergoing genetic testing (Deruelle et al., 2023; Macalino et al., 2023). However, some challenges were exacerbated such as the exclusion of patients without reliable access to the internet or technological literacy to utilize telemedicine (Mann et al., 2021). Insurance payor limitations may also restrict the effectiveness of genetic services as they may stipulate narrow coverage guidelines (Amendola et al., 2019; Suther & Kiros, 2009). Additional strain can be observed in obtaining an appropriate genetics referral due to the lack of familiarity with genetic indications or limited accessibility of genetics providers outside of large medical centers. Intentional and structured collaboration between genetics and nongenetics providers can be effective at bridging this gap (Morrow et al., 2023; Truong et al., 2021). Lastly, genetics studies have had suboptimal inclusion of nonwhite populations which contributes to difficulty interpreting the genetic findings in diverse populations without the diverse background population data to serve as a control (Appelbaum et al., 2022; Fine et al., 2005; Gerido et al., 2023; Glenn et al., 2012).

5 | CONCLUSION

To date, there are 593 pathogenic or likely pathogenic *RPGR* variants registered in ClinVar, and *RPGR* variants are noted to be causal in 15%–20% of all individuals with retinitis pigmentosa cases (Branham et al., 2012; Shu et al., 2005). Thus, *RPGR* should be considered a first-tier gene when screening males with retinal dystrophy consistent with X-linked inheritance. In the clinic, it may be difficult to discern a clear X-linked recessive pattern with a limited number of affected family members especially in the presence of affected females. Such pedigrees can also suggest an autosomal dominant inheritance with variable expressivity and incomplete penetrance. In this report, we highlight how a comprehensive retinal disorders gene panel from a major commercial genetics laboratory ordered in 2021 did not include *RPGR*. Access to more comprehensive genetic

testing such as ES is important for the diagnosis of genetic disorders especially when considering diseases that have a short window in which curative genomic therapies can be implemented. Our report highlights the need for close consideration of gene inclusion on panels both for laboratories and for clinicians who order genetics testing.

AUTHOR CONTRIBUTIONS

R.J.G., B.V. wrote the first draft of the manuscript. L.S., S.N. recruited the human subject and provided clinical evaluation. L.V., N.O. performed and interpreted the exome sequencing. R.A.L. provided ophthalmic evaluation and photographs. M.F.W., S.N. oversaw the project. All authors edited and contributed to the final draft.

ACKNOWLEDGMENTS

First and foremost, we would like to recognize the research participant for his crucial role in our research of genetic disease. This work was supported by the Texome Project which is funded by the National Human Genome Research Institute (NHGRI) under R01HG011795. The Texome Project also receives philanthropic funding through the Jan and Dan Duncan Neurological Research Institute of Texas Children's Hospital. This work was supported in part by funding of The Baylor College of Medicine Intellectual and Developmental Disabilities Research Center (P50HD103555) from the Eunice Kennedy Shriver NICHD. The contents of this publication do not necessarily reflect the views or policies of the NIH. The mention of trade names, commercial products, or organizations do not imply endorsement by the US Government. A full list of collaborators is provided in Supplemental Table S2.

CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

Variant level data from this report are available on Clinvar at reference number: SCV002574700.1.

ETHICS STATEMENT

Consent for participation in clinical research and publication was obtained from the individual presented in this case report. The Texome Project protocol has been reviewed and approved for use with human subjects by the Baylor College of Medicine Institutional Review Board (Protocol # H-49277).

ORCID

Ryan J. German  <https://orcid.org/0000-0001-8193-7329>

REFERENCES

- Amendola, L. M., Hart, M. R., Bennett, R. L., Horike-Pyne, M., Dorschner, M., Shirts, B., & Jarvik, G. P. (2019). Insurance coverage does not predict outcomes of genetic testing: The search for meaning in payer decisions for germline cancer tests. *Journal of Genetic Counseling*, 28(6), 1208–1213. <https://doi.org/10.1002/jgc4.1155>
- Appelbaum, P. S., Burke, W., Parens, E., Zeevi, D. A., Arbour, L., Nanibaa'A, G., Bonham, V. L., & Chung, W. K. (2022). Is there a way to reduce the inequity in variant interpretation on the basis of ancestry? *American Journal of Human Genetics*, 109(6), 981–988. <https://doi.org/10.1016/j.ajhg.2022.04.012>
- Ayyagari, R., Demirci, F. Y., Liu, J., Bingham, E. L., Stringham, H., Kakuk, L. E., Boehnke, M., Gorin, M. B., Richards, J. E., & Sieving, P. A. (2002). X-linked recessive atrophic macular degeneration from RPGR mutation. *Genomics*, 80(2), 166–171. <https://doi.org/10.1006/geno.2002.6815>
- Bertelsen, M., Linneberg, A., & Rosenberg, T. (2015). Socio-economic characteristics of patients with generalized retinal dystrophy in Denmark. *Acta Ophthalmologica*, 93(2), 134–140. <https://doi.org/10.1111/aos.12467>
- Branham, K., Othman, M., Brumm, M., Karoukis, A. J., Atmacasonmez, P., Yashar, B. M., Schwartz, S. B., Stover, N. B., Trzupke, K., Wheaton, D., Jennings, B., Ciccarelli, M. L., Jayasundera, K. T., Lewis, R. A., Birch, D., Bennett, J., Sieving, P. A., Andreasson, S., Duncan, J. L., ... Swaroop, A. (2012). Mutations in RPGR and RP2 account for 15% of males with simplex retinal degenerative disease. *Investigative Ophthalmology & Visual Science*, 53(13), 8232–8237. <https://doi.org/10.1167/iovs.12-11025>
- Chaumet-Riffaud, A. E., Chaumet-Riffaud, P., Cariou, A., Devisme, C., Audo, I., Sahel, J. A., & Mohand-Said, S. (2017). Impact of retinitis pigmentosa on quality of life, mental health, and employment among young adults. *American Journal of Ophthalmology*, 177, 169–174. <https://doi.org/10.1016/j.ajo.2017.02.016>
- Chivers, M., Li, N., Pan, F., Wieffer, H., Slowik, R., & Leartsakulpanitch, J. (2021). The burden of X-linked retinitis pigmentosa on patients and society: A narrative literature review. *ClinicoEconomics and Outcomes Research*, 13, 565–572. <https://doi.org/10.2147/CEOR.S297287>
- Chou, A. F., Duncan, A. R., Hallford, G., Kelley, D. M., & Dean, L. W. (2021). Barriers and strategies to integrate medical genetics and primary care in underserved populations: A scoping review. *Journal of Community Genetics*, 12(3), 291–309. <https://doi.org/10.1007/s12687-021-00508-5>
- Cross, N., van Steen, C., Zegaoui, Y., Satherley, A., & Angelillo, L. (2022). Current and future treatment of retinitis pigmentosa. *Clinical Ophthalmology*, 16, 2909–2921. <https://doi.org/10.2147/OPTH.S370032>
- Demirci, F. Y. K., Rigatti, B. W., Wen, G., Radak, A. L., Mah, T. S., Baic, C. L., Traboulsi, E. I., Alitalo, T., Ramser, J., & Gorin, M. B. (2002). X-linked cone-rod dystrophy (locus COD1): Identification of mutations in RPGR exon ORF15. *American Journal of Human Genetics*, 70(4), 1049–1053. <https://doi.org/10.1086/339620>
- Deruelle, T., Kalouguina, V., Trein, P., & Wagner, J. (2023). Is there a “pandemic effect” on individuals’ willingness to take genetic tests? *European Journal of Human Genetics*, 31(3), 360–362. <https://doi.org/10.1038/s41431-022-01223-6>
- Di Iorio, V., Karali, M., Melillo, P., Testa, F., Brunetti-Pierri, R., Musacchia, F., Condroyer, C., Neidhardt, J., Audo, I., Zeitz, C., Banfi, S., & Simonelli, F. (2020). Spectrum of disease severity in patients with X-linked retinitis pigmentosa due to RPGR mutations. *Investigative Ophthalmology & Visual Science*, 61(14), 36. <https://doi.org/10.1167/iovs.61.14.36>
- El Naofal, M., Ramaswamy, S., Alsarhan, A., Nugud, A., Sarfraz, F., Janbaz, H., Taylor, A., Jain, R., Halabi, N., Yaslam, S., Alfalasi, R., Shenbagam, S., Rabea, F., Bitzan, M., Yavuz, L., Wafadari, D., Abulhoul, H., Shankar, S., Al Maazmi, M., ... Abou Tayoun, A. N. (2023). The genomic landscape of rare disorders in the Middle East. *Genome Medicine*, 15(1), 5. <https://doi.org/10.1186/s13073-023-01157-8>
- Fine, M. J., Ibrahim, S. A., & Thomas, S. B. (2005). The role of race and genetics in health disparities research. *American Journal of Public Health*, 95(12), 2125–2128. <https://doi.org/10.2105/AJPH.2005.076588>
- Georgiou, M., Awadh Hashem, S., Daich Varela, M., & Michaelides, M. (2021). Gene therapy in X-linked retinitis pigmentosa due to defects in RPGR. *International Ophthalmology Clinics*, 61(4), 97–108. <https://doi.org/10.1097/IIO.0000000000000384>
- Gerido, L. H., Resnicow, K., Stoffel, E., Tomlin, T., Cook-Deegan, R., Cline, M., Coffin, A., Holdren, J., Majumder, M. A., & He, Z. (2023). Big advocacy, little recognition: The hidden work of black patients in precision medicine. *Journal of Community Genetics*, 14(6), 657–665. <https://doi.org/10.21203/rs.3.rs-2340760/v1>
- Ghosh, A. K., Murga-Zamalloa, C. A., Chan, L., Hitchcock, P. F., Swaroop, A., & Khanna, H. (2010). Human retinopathy-associated ciliary protein retinitis pigmentosa GTPase regulator mediates cilia-dependent vertebrate development. *Human Molecular Genetics*, 19(1), 90–98. <https://doi.org/10.1093/hmg/ddp469>
- Glenn, B. A., Chawla, N., & Bastani, R. (2012). Barriers to genetic testing for breast cancer risk among ethnic minority women: An exploratory study. *Ethnicity & Disease*, 22(3), 267–273.
- Hanany, M., Rivolta, C., & Sharon, D. (2020). Worldwide carrier frequency and genetic prevalence of autosomal recessive inherited retinal diseases. *Proceedings of the National Academy of Sciences*, 117(5), 2710–2716. <https://doi.org/10.1073/pnas.1913179117>
- Heath Jeffery, R. C., Mukhtar, S. A., McAllister, I. L., Morgan, W. H., Mackey, D. A., & Chen, F. K. (2021). Inherited retinal diseases are the most common cause of blindness in the working-age population in Australia. *Ophthalmic Genetics*, 42(4), 431–439. <https://doi.org/10.1080/13816810.2021.1913610>
- Khanna, H., Hurd, T. W., Lillo, C., Shu, X., Parapuram, S. K., He, S., Akimoto, M., Wright, A. F., Margolis, B., Williams, D. S., & Swaroop, A. (2005). RPGR-ORF15, which is mutated in retinitis pigmentosa, associates with SMC1, SMC3, and microtubule transport proteins. *The Journal of Biological Chemistry*, 280(39), 33580–33587. <https://doi.org/10.1074/jbc.M505827200>
- Macalino, A. J., Porter, R. S., Smith, L., Wang, H., & Levin, A. V. (2023). A study of disparities in access to genetic care pre- and post-pandemic. *American Journal of Medical Genetics. Part A*, 191, 1704–1710. <https://doi.org/10.1002/ajmg.a.63191>
- Maggi, J., Roberts, L., Koller, S., Rebello, G., Berger, W., & Ramesar, R. (2020). De novo assembly-based analysis of RPGR exon ORF15 in an indigenous African cohort overcomes limitations

- of a standard next-generation sequencing (NGS) data analysis pipeline. *Genes (Basel)*, 11(7), 800. <https://doi.org/10.3390/genes11070800>
- Mann, C., Goodhue, B., Guillard, A., Slamon, J., Newman, R., Zhao, Z., Ding, T., Petrelli, G., & Dudek, M. (2021). The COVID-19 pandemic and reproductive genetic counseling: Changes in access and service delivery at an academic medical center in the United States. *Journal of Genetic Counseling*, 30(4), 958–968. <https://doi.org/10.1002/jgc4.1462>
- Mihailovic, N., Schimpf-Linzenbold, S., Sattler, I., Eter, N., & Heiduschka, P. (2022). The first reported case of a deletion of the entire RPGR gene in a family with X-linked retinitis pigmentosa. *Ophthalmic Genetics*, 43(5), 679–684. <https://doi.org/10.1080/13816810.2022.2083181>
- Moreno-Leon, L., West, E. L., O'Hara-Wright, M., Li, L., Nair, R., He, J., Anand, M., Sahu, B., Chavali, V. R. M., Smith, A. J., Ali, R. R., Jacobson, S. G., Cideciyan, A. V., & Khanna, H. (2021). RPGR isoform imbalance causes ciliary defects due to exon ORF15 mutations in X-linked retinitis pigmentosa (XLRP). *Human Molecular Genetics*, 29(22), 3706–3716. <https://doi.org/10.1093/hmg/ddaa269>
- Morrow, A., Steinberg, J., Chan, P., Tiernan, G., Kennedy, E., Egoroff, N., Hilton, D., Sankey, L., Venchiarutti, R., Hayward, A., Pearn, A., McKay, S., Debono, D., Hogden, E., & Taylor, N. (2023). In person and virtual process mapping experiences to capture and explore variability in clinical practice: Application to genetic referral pathways across seven Australian hospital networks. *Translational Behavioral Medicine*, 13, 561–570. <https://doi.org/10.1093/tbm/ibad009>
- Muth, A., Crona, J., Gimm, O., Elmgren, A., Filipsson, K., Stenmark Askmalm, M., Sandstedt, J., Tengvar, M., & Tham, E. (2019). Genetic testing and surveillance guidelines in hereditary pheochromocytoma and paraganglioma. *Journal of Internal Medicine*, 285(2), 187–204. <https://doi.org/10.1111/joim.12869>
- Nanda, A., Salvetti, A. P., Clouston, P., Downes, S. M., & MacLaren, R. E. (2018). Exploring the variable phenotypes of RPGR carrier females in assessing their potential for retinal gene therapy. *Genes (Basel)*, 9(12), 643. <https://doi.org/10.3390/genes9120643>
- National Academies of Sciences, Engineering, and Medicine, Health and Medicine Division, Board on Health Sciences Policy, Roundtable on Genomics and Precision Health. (2018). *Understanding disparities in access to genomic medicine: Proceedings of a workshop*. National Academies Press. <https://doi.org/10.17226/25277>
- Nguyen, X.-T.-A., Talib, M., van Schooneveld, M. J., Brinks, J., ten Brink, J., Florijn, R. J., Wijnholds, J., Verdijk, R. M., Bergen, A. A., & Boon, C. J. F. (2020). RPGR-associated dystrophies: Clinical, genetic, and histopathological features. *International Journal of Molecular Sciences*, 21(3), 835. <https://doi.org/10.3390/ijms21030835>
- O'Brien, G., Christensen, K. D., Sullivan, H. K., Stout, N. K., Diller, L., Yeh, J. M., & Wu, A. C. (2021). Estimated cost-effectiveness of genetic testing in siblings of newborns with cancer susceptibility gene variants. *JAMA Network Open*, 4(10), e2129742. <https://doi.org/10.1001/jamanetworkopen.2021.29742>
- Reuter, C. M., Kohler, J. N., Bonner, D., Zastrow, D., Fernandez, L., Dries, A., Marwaha, S., Davidson, J., Brokamp, E., Herzog, M., Hong, J., Macnamara, E., Rosenfeld, J. A., Schoch, K., Spillmann, R., Undiagnosed Diseases Network, Loscalzo, J., Krier, J., Stoler, J., ... Wheeler, M. T. (2019). Yield of whole exome sequencing in undiagnosed patients facing insurance coverage barriers to genetic testing. *Journal of Genetic Counseling*, 28(6), 1107–1118. <https://doi.org/10.1002/jgc4.1161>
- Richards, S., Aziz, N., Bale, S., Bick, D., Das, S., Gastier-Foster, J., Grody, W. W., Hegde, M., Lyon, E., Spector, E., Voelkerding, K., Rehm, H. L., & ACMG Laboratory Quality Assurance Committee. (2015). Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genetics in Medicine*, 17, 405–424. <https://doi.org/10.1038/gim.2015.30>
- Roepman, R., van Duijnhoven, G., Rosenberg, T., Pinckers, A. J., Bleeker-Wagemakers, L. M., Bergen, A. A., Post, J., Beck, A., Reinhardt, R., Ropers, H. H., Cremers, F. P., & Berger, W. (1996). Positional cloning of the gene for X-linked retinitis pigmentosa 3: Homology with the guanine-nucleotide-exchange factor RCC1. *Human Molecular Genetics*, 5(7), 1035–1041. <https://doi.org/10.1093/hmg/5.7.1035>
- Sandberg, M. A., Rosner, B., Weigel-DiFranco, C., Dryja, T. P., & Berson, E. L. (2007). Disease course of patients with X-linked retinitis pigmentosa due to RPGR gene mutations. *Investigative Ophthalmology & Visual Science*, 48(3), 1298–1304. <https://doi.org/10.1167/iovs.06-0971>
- Schoch, K., Esteves, C., Bican, A., Spillmann, R., Cope, H., McConkie-Rosell, A., Walley, N., Fernandez, L., Kohler, J. N., Bonner, D., Reuter, C., Stong, N., Mulvihill, J. J., Novacic, D., Wolfe, L., Abdelbaki, A., Toro, C., Tiffit, C., Malicdan, M., ... Shashi, V. (2021). Clinical sites of the Undiagnosed Diseases Network: Unique contributions to genomic medicine and science. *Genetics in Medicine*, 23(2), 259–271. <https://doi.org/10.1038/s41436-020-00984-z>
- Serrano, J. G., O'Leary, M., VanNoy, G., Holm, I. A., Fraiman, Y. S., Rehm, H. L., O'Donnell-Luria, A., & Wojcik, M. H. (2023). Advancing understanding of inequities in rare disease genomics. *medRxiv*. <https://doi.org/10.1101/2023.03.28.23286936>
- Shu, X., Fry, A. M., Tulloch, B., Manson, F. D. C., Crabb, J. W., Khanna, H., Faragher, A. J., Lennon, A., He, S., Trojan, P., Giessl, A., Wolfrum, U., Vervoort, R., Swaroop, A., & Wright, A. F. (2005). RPGR ORF15 isoform co-localizes with RPGRIP1 at centrioles and basal bodies and interacts with nucleophosmin. *Human Molecular Genetics*, 14(9), 1183–1197. <https://doi.org/10.1093/hmg/ddi129>
- Suther, S., & Kiros, G.-E. (2009). Barriers to the use of genetic testing: A study of racial and ethnic disparities. *Genetics in Medicine*, 11(9), 655–662. <https://doi.org/10.1097/GIM.0b013e3181ab22aa>
- Talib, M., van Schooneveld, M. J., Thiadens, A. A., Fiocco, M., Wijnholds, J., Florijn, R. J., Schalij-Delfos, N. E., van Genderen, M. M., Putter, H., Cremers, F. P. M., Dagnelie, G., ten Brink, J. B., Klaver, C. C. W., van den Born, L. I., Hoyng, C. B., Bergen, A. A., & Boon, C. J. F. (2019). Clinical and genetic characteristics of male patients with RPGR-associated retinal dystrophies: A long-term follow-up study. *Retina (Philadelphia, PA)*, 39(6), 1186–1199. <https://doi.org/10.1097/IAE.0000000000002125>
- Truong, T. K., Kenneson, A., Rosen, A. R., & Singh, R. H. (2021). Genetic referral patterns and responses to clinical scenarios:

- A survey of primary care providers and clinical geneticists. *Journal of Primary Care & Community Health*. <https://doi.org/10.1177/21501327211046734>
- Tuupanen, S., Gall, K., Sistonen, J., Saarinen, I., Kämpjärvi, K., Wells, K., Merkkiniemi, K., von Nandelstadh, P., Sarantaus, L., Käsäkoski, J., Mårtenson, E., Västinsalo, H., Schleit, J., Sankila, E. M., Kere, A., Junnila, H., Siivonen, P., Andreevskaya, M., Kytölä, V., ... Alastalo, T. P. (2022). Prevalence of RPGR-mediated retinal dystrophy in an unselected cohort of over 5000 patients. *Translational Vision Science & Technology*, *11*(1), 6. <https://doi.org/10.1167/tvst.11.1.6>
- Vervoort, R., Lennon, A., Bird, A. C., Tulloch, B., Axton, R., Miano, M. G., Meindl, A., Meitinger, T., Ciccodicola, A., & Wright, A. F. (2000). Mutational hot spot within a new RPGR exon in X-linked retinitis pigmentosa. *Nature Genetics*, *25*(4), 462–466. <https://doi.org/10.1038/7818>
- Watanabe, K., Hiratsuka, Y., Yamamoto, S., & Murakami, A. (2023 Mar 30). Economic impacts and quality of life for caregivers of patients with retinitis pigmentosa: A cross-sectional Japanese study. *Healthcare (Basel)*, *11*(7), 988. <https://doi.org/10.3390/healthcare11070988>
- Wiener, E. K., Buchanan, J., Krause, A., Lombard, Z., & DDD-Africa Study, as members of the H3Africa Consortium. (2023). Retrospective file review shows limited genetic services fails most patients - an argument for the implementation of exome sequencing as a first-tier test in resource-constraint settings. *Orphanet Journal of Rare Diseases*, *18*, 81. <https://doi.org/10.1186/s13023-023-02642-4>
- Zito, I., Downes, S. M., Patel, R. J., Cheetham, M. E., Ebenezer, N. D., Jenkins, S. A., Bhattacharya, S. S., Webster, A. R., Holder, G. E., Bird, A. C., Bamiou, D. E., & Hardcastle, A. J. (2003). RPGR mutation associated with retinitis pigmentosa, impaired hearing, and sinorespiratory infections. *Journal of Medical Genetics*, *40*(8), 609–615. <https://doi.org/10.1136/jmg.40.8.609>
- Zou, X., Fang, S., Wu, S., Li, H., Sun, Z., Zhu, T., Wei, X., & Sui, R. (2020). Detailed comparison of phenotype between male patients carrying variants in exons 1–14 and ORF15 of RPGR. *Experimental Eye Research*, *198*, 108147. <https://doi.org/10.1016/j.exer.2020.108147>

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: German, R. J., Vuocolo, B., Vossaert, L., Owen, N., Lewis, R. A., Saba, L.; Wangler, M. F., & Nagamani, S. (2024). Novel hemizygous single-nucleotide duplication in *RPGR* in a patient with retinal dystrophy and sensorineural hearing loss. *Molecular Genetics & Genomic Medicine*, *12*, e2404. <https://doi.org/10.1002/mgg3.2404>