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Received: 4 October 2022 | Revised: 6 February 2023 | Accepted: 12 February 2023

DOI: 10.1111/cge.14312

CLINICAL GENETICS WILEY

SHORT REPORT

Variants of *LRP2*, encoding a multifunctional cell-surface endocytic receptor, associated with hearing loss and retinal dystrophy

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Abstract

Hereditary deafness and retinal dystrophy are each genetically heterogenous and clinically variable. Three small unrelated families segregating the combination of deafness and retinal dystrophy were studied by exome sequencing (ES). The proband of Family 1 was found to be compound heterozygous for NM_004525.3: *LRP2*: c.5005A > G, p.(Asn1669Asp) and c.149C > G, p.(Thr50Ser). In Family 2, two sisters were found to be compound heterozygous for *LRP2* variants, p.(Tyr3933Cys) and an experimentally confirmed c.7715 + 3A > T consensus splice-altering variant. In Family 3, the proband is compound heterozygous for a consensus donor splice site variant

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Funding information
African Academy of Sciences; National Human Genome Research Institute, Grant/Award Number: U01-HG-009716; NIDCD, Grant/Award Numbers: DIR DC000088, DC000039, DC000060, DC000086, R01s DC01165, DC003594, DC016593, DC017712; NIDCR Genomics and Computational Biology Core; Wellcome Trust, Grant/Award Numbers: 107755Z/15/Z, H3A/18/001

LRP2: c.8452_8452 + 1del and p.(Cys3150Tyr). In mouse cochlea, *Lrp2* is expressed abundantly in the stria vascularis marginal cells demonstrated by smFISH, single-cell and single-nucleus RNAseq, suggesting that a deficiency of LRP2 may compromise the endocochlear potential, which is required for hearing. *LRP2* variants have been associated with Donnai–Barrow syndrome and other multisystem pleiotropic phenotypes different from the phenotypes of the four cases reported herein. Our data expand the phenotypic spectrum associated with pathogenic variants in *LRP2* warranting their consideration in individuals with a combination of hereditary hearing loss and retinal dystrophy.

KEYWORDS
deafness, Donnai–Barrow syndrome, *LRP2*, megalin, retinal dystrophy, RNAseq, stria vascularis

1 | INTRODUCTION

Multiple pathogenic mechanisms and numerous genes are associated with deafness or retinal dystrophy.[1,2] There are also monogenic syndromes including loss of hearing and vision. Usher syndrome (USH, OMIM 276900) is one such example and is the most common deaf-blindness disorder. USH is genetically and clinically heterogenous and associated with variants of several different genes[3] (Table S1). Atypical USH shows deviations in either retinal, auditory, or vestibular aspects.[3,4] Stickler syndrome (STL) is also characterized by clinically variable vision and hearing loss as well as skeletal abnormalities.[5] This study included three small families presenting with hereditary deafness and retinal dystrophy for whom we did not identify biallelic pathogenic variants in any of the USH or STL-associated genes.[3,5] Exome sequencing (ES) of probands' genomic DNA revealed biallelic compound heterozygous variants of *LRP2* (OMIM 600073) encoding LRP2, the low-density lipoprotein receptor related protein 2 (a.k.a. megalin), an evolutionarily conserved multifunctional cell-surface endocytic receptor of the low-density lipoprotein receptor (LDLR) family.[6]

2 | MATERIALS AND METHODS

Informed consent was obtained from participants as approved by the Combined NIH IRB for National Eye Institute (NEI) protocols 05-EI-0096 and 08-EI-0102. Extensive clinical and molecular genetic data and experimental methods are available in Data S1.

3 | RESULTS

The Family 1 proband is the only child of unrelated, unaffected parents of European ancestry, who report no family history of hearing or vision loss. The proband has a profound sensorineural hearing loss and has two cochlear implants (Figures 1A and S1A). Vestibular areflexia was detected as bilaterally absent cervical vestibular evoked myogenic potentials and no vestibular contribution to postural stability was measured on computerized dynamic platform posturography.[3] Electroretinography performed at 14 years of age was consistent with rod-cone degeneration with severely reduced rod and cone amplitudes and an electronegative scotopic combined response, myopic astigmatism, and a severe color vision deficit.

Two sisters of Family 2 were ascertained at the Dayton Children's Hospital in Ohio (Figure 1B). The older sister's recent examination at 12 years old noted a corrected visual acuity of 20/200 in both eyes. She was diagnosed with advanced myopic degeneration, retinal dystrophy bilaterally, and mild juvenile cataracts in both eyes. She passed newborn hearing screening but was subsequently diagnosed with sensorineural hearing loss (Figure S1). The younger sister of Family 2 was seen as a 6 years old at the Dayton Children's Hospital and has bilateral high myopia and right eye esotropia as a 1 year old. Retinal dystrophy and advanced myopic degeneration bilaterally were also noted (Figure S2). Due to reports of proteinuria associated with variants of *LRP2*, renal evaluation was pursued for both siblings, which revealed persistent proteinuria.[8]

The proband from Family 3 was 16 years old at the time of her presentation to the NEI/NIH (Figure 1C,D). She had proteinuria and a history of high myopia since infancy and had undergone surgical correction (scleral buckle, pars plana vitrectomy, and laser retinopexy) of a left eye retinal detachment, cataract extraction and intraocular lens placement (Figure S2).

Parents and proband of Family 1 were studied by ES (Figure 1). Biallelic pathogenic variants were not detected in USH-associated genes (Tables S1 and S2) or in genes associated with nonsyndromic deafness itemized on the HHLHP (https://hereditaryhearingloss.org). However, two deleterious variants of *LRP2* were identified in trans-configuration (RefSeq ID NM_004525.3: c.149C > G, p.(Thr50Ser) in exon 2 and c.5005A > G, p.(Asn1669Asp) in exon 30), confirmed by Sanger sequencing and co-segregated with the phenotype as recessive variants (Figures 1A and S1A). The p.(Asn1669Asp) variant is predicted to be damaging by multiple *in silico* tools (Table S3). The p.(Thr50Ser) and p.(Asn1669Asp) are located in the extracellular LDLR class A and B domains, respectively. The human Thr-50 and Asn-1669 residues are well conserved among species (Figure 1F). Perhaps these variants influence ligand binding in LDLR class A and B domains of LRP2. Estrogen binds LRP2 in the inner ear, and estrogen transport reduction may cause a hearing loss.[9,10]

Compound heterozygous *LRP2* variants were detected in both sisters of Family 2 (Figure 1B) c.11798A > G in exon 63,

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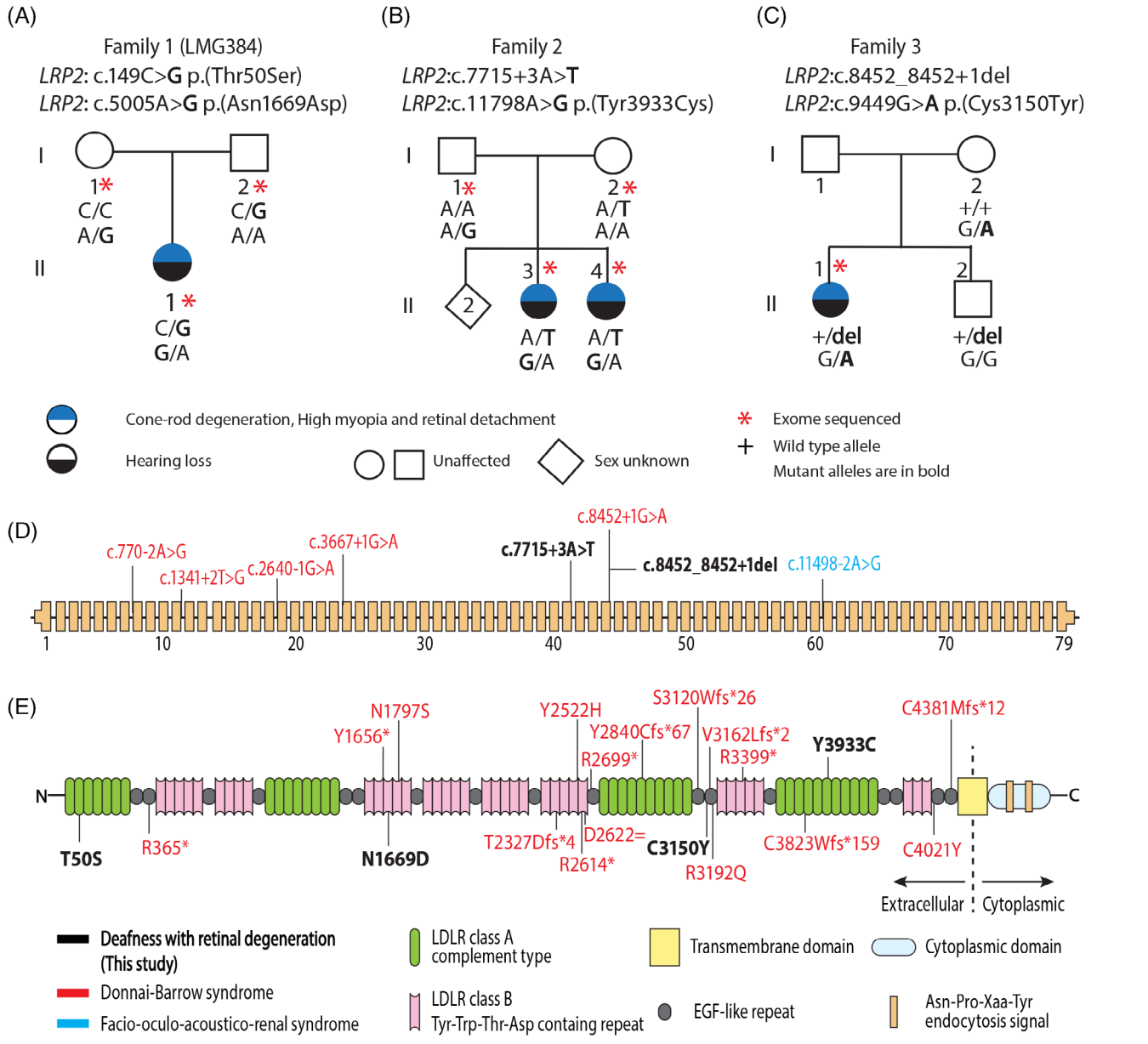

FIGURE 1 Hearing loss and retinal dystrophy associated with *LRP2* variants. (A–C) Pedigrees of Families 1, 2, and 3. (D) The 79 coding exons of *LRP2* and locations of reported splice variants. (E) Protein domains of LRP2 protein (RefSeq ID NP_004516.2) with reported missense variants (modified from Kantarci et al.[7]). (F) Conservation of human Thr-50, Asn-1669, Cys-3150, and Tyr-3933 residues in LRP2 orthologues (RefSeq ID: Human, NP_004516.2; Chimp, XP_009441920.3; Rhesus, XP_014965780.2; Mouse, NP_001074557.1; Rat, NP_110454.2; Platypus, XP_028927340.1; Zebrafish, NP_001181916.1). [Colour figure can be viewed at wileyonlinelibrary.com]

p.(Tyr3933Cys) and a novel predicted splice site variant c.7715 + 3A > T in intron 41. Both variants are absent from gnomAD (Table S3) and are predicted to be damaging. The c.7715 + 3A > T variant is predicted to disrupt the *LRP2* exon 41 consensus donor splice site by Splice AI, Human Splice Finder, NetGene2 and Alternative Splice Site Predictor, which was experimentally confirmed by a mini-gene

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splicing assay (Figure S4). The proband of Family 3 was diagnosed with a hearing loss and retinopathy. She is compound heterozygous for a consensus splice site variant *LRP2*: c.8452_8452 + 1del and c.9449G > A, p.(Cys3150Tyr, CADD 25.7) (Figures 1C and S1C).

In mouse, *Lrp2* mRNA is expressed in the stria vascularis (SV) marginal cells, Reissner's membrane and spindle cells (Figure S4D), consistent with immunofluorescence localization of LRP2.[11] Our scRNA and snRNA-seq data show expression of *Lrp2* predominantly in SV marginal cells (Figure S4E).

4 | DISCUSSION

The longest human LRP2 isoform has 4655 residues encoded by 79 exons (UniProtKB P98164). LRP2 has 4398 extracellular residues which interact with a variety of ligands, a transmembrane domain and a small intracellular cytoplasmic domain at the C-terminus containing an endocytosis signal sequence[12] (Figure 1E). LRP2 is internalized upon ligand-binding, controlling functions such as lipoprotein metabolism and endocytic uptake in kidney. LRP2 also modulates sonic hedgehog signaling in mouse and is required for normal development of the inner ear and eye.[13] Additionally, in SV marginal cells, LRP2 is the receptor for aminoglycoside, which is cytotoxic to inner hair cells.[14]

Our RNAseq data suggest a defect in the SV leading to hearing loss in patients with *LRP2* mutations. The SV generates the +80 millivolt endocochlear potential driving sound transduction, which may be compromised by biallelic *LRP2* variants, suggesting an unreported combination of a strial defect with retinal dystrophy to account for the deaf-blindness phenotype.

Variants of human *LRP2* are associated with a panoply of clinically complex disorders (Table S4, Figure S3) including Donnai–Barrow syndrome (DBS, OMIM 222448) characterized by severe myopia, iris coloboma or retinal detachment, sensorineural hearing loss, intellectual disability, craniofacial malformations, agenesis of the corpus callosum (ACC), congenital diaphragmatic hernia (CDH), and omphalocele.[7] This phenotypic spectrum indicates functions for LRP2 in many organs (Figures 1D,E and S3). Twenty-three different variants distributed across *LRP2* are associated with DBS and most are loss of function alleles (DVD). However, our study probands do not display craniofacial dysmorphology, ACC or CDH suggesting that one of the two variants of *LRP2* segregating in each of the three studied families must not fully disable LRP2 function, acting as hypomorphic alleles associated with a more limited deaf-blindness phenotype.

A plausible hypomorphic allele in the Family 1 proband is *LRP2* p.(Thr50Ser). There are five p.(Thr50Ser) homozygotes of Finnish ancestry in gnomAD data (v3.1.2). Their hearing and visual status are unknown. ACMG/AMP recommends excluding bottlenecked founder populations including Finnish Europeans as a filtering population where pathogenic allele frequencies may rise above 5%. Moreover, in gnomAD there are 95 individuals homozygous for *GJB2* variant p.(Glu114Gly) associated convincingly with recessive deafness *DFNB1*, 39 homozygotes for *CDH23*: p.(Val475Met), and 24 homozygotes for *SLC26A4*: p.(Asn324Tyr).

LRP2 p.(Thr50Ser) has a CADD score of 20.2 suggesting pathogenicity. Nevertheless, we considered two possibilities. p.(Thr50Ser) is a benign variant in disequilibrium with a pathogenic recessive variant elsewhere in *LRP2* gene that was not detected by ES analysis, although we had adequate ES coverage for all 79 exons of *LRP2*. Alternatively, p.(Thr50Ser) is pathogenic when in trans with a more disabling variant of *LRP2* such as p.(Asn1669Asp). There are examples of hypomorphic risk alleles that are pathogenic only in compound heterozygosity with a damaging variant.[15] For example, the noncoding CEVA SNP haplotype has a 5.6% carrier frequency in controls of European ancestry, is located upstream of the first exon of an otherwise wild-type *SLC26A4* gene, and is associated with enlarged vestibular aqueduct when in trans with a pathogenic *SLC26A4* variant.[16]

The conditional silencing of mouse *Lrp2* expression in developing ocular tissue caused high myopia and a decrease in bipolar, photoreceptor and retinal ganglion cells, similar to the *lrp2 bugeye* phenotype in zebrafish.[17] Homozygous *Lrp2* knockout mice typically die from respiratory failure, but a few survive to adulthood.[18] Survivors display brain malformations including forebrain fusion, a common ventricular system, lack of the olfactory bulb and enlarged eyes typical of high myopia and are deaf at 3 months of age further demonstrating the importance of LRP2 in the mammalian eye and ear.[9]

Data from cohorts of 153 nonsyndromic and syndromic deaf probands from Ghana, 500 families from Pakistan and a multi-ethnic North American cohort of 50 families screened with ES and 654 probands screened with a targeted deafness-gene panel did not yield additional biallelic pathogenic variants of *LRP2* associated with deaf-blindness. Thus, variants of *LRP2* appear to be a rare cause of human deaf-blindness in these populations. Nevertheless, the clinical and genetic data of the three unrelated probands reported here and the phenotype of the *Lrp2* mutant mouse emphasize the need to evaluate *LRP2* sequence in individuals with hearing loss and retinal dystrophy.[2]

AUTHOR CONTRIBUTIONS

Thomas B. Friedman, Rabia Faridi, Sayaka Inagaki, Wadih M. Zein, and Carmen C. Brewer planned the study and wrote the first draft. Amy E. Turriff, Elvis Twumasi Aboagye, Keith Pelstring, Bin Guan, Amelia Naik, Robert B. Hufnagel, Amanda G. Noyes, Laura A. G. Sulmonte, Wadih M. Zein, J. Karl de Dios, Wadih M. Zein, Rizwan Yousaf, Shoujun Gu, Michael Hoa, Robert J. Morell recruited subjects and did data analyses. Sheikh Riazuddin, Suzanne M. Leal, Isabelle Schrauwen, Ambroise Wonkam, Samuel Mawuli Adadey, Ekaterini Tsilou, Gordon A. Awandare, and Hela Azaiez screened cohorts for *LRP2* variants. All authors read and approved the final manuscript.

ACKNOWLEDGMENTS

We thank the families for participation in this study, and Drs. Roux, Hertzano, and Olszewski for evaluating the manuscript. This study utilized the high-performance computational capabilities of the Biowulf Linux cluster at the NIH (http://biowulf.nih.gov).

FUNDING INFORMATION

Funded (in part) by the NIDCD, DIR DC000088 to Michael Hoa, DC000039 to Thomas B. Friedman, DC000060 to Andrew J. Griffith, DC000086 to Robert J. Morell, NIDCD/NIDCR Genomics and Computational Biology Core, Wellcome Trust 107755Z/15/Z to Gordon A.

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Awandare and Ambroise Wonkam, NHGRI/NIH U01-HG-009716, African Academy of Science/Wellcome Trust H3A/18/001 to Ambroise Wonkam, and NIDCD R01s DC01165, DC003594, DC016593 and DC017712 to Suzanne M. Leal.

CONFLICT OF INTEREST STATEMENT

The authors declare there is no potential conflict of interest.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/cge.14312.

DATA AVAILABILITY STATEMENT

Variants identified here are in Clinvar (https://www.ncbi.nlm.nih.gov/clinvar/) SUB12100712, SUB12101044, SUB12114010, SUB12114033, SUB11119334.

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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: Faridi R, Yousaf R, Gu S, et al. Variants of *LRP2*, encoding a multifunctional cell-surface endocytic receptor, associated with hearing loss and retinal dystrophy. *Clinical Genetics*. 2023;103(6):699-703. doi:10.1111/cge.14312

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