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King Salman Center For Disability Research
Science Benefiting People
علم ينفع الناس

Scientific Report 2018

Science Benefiting People

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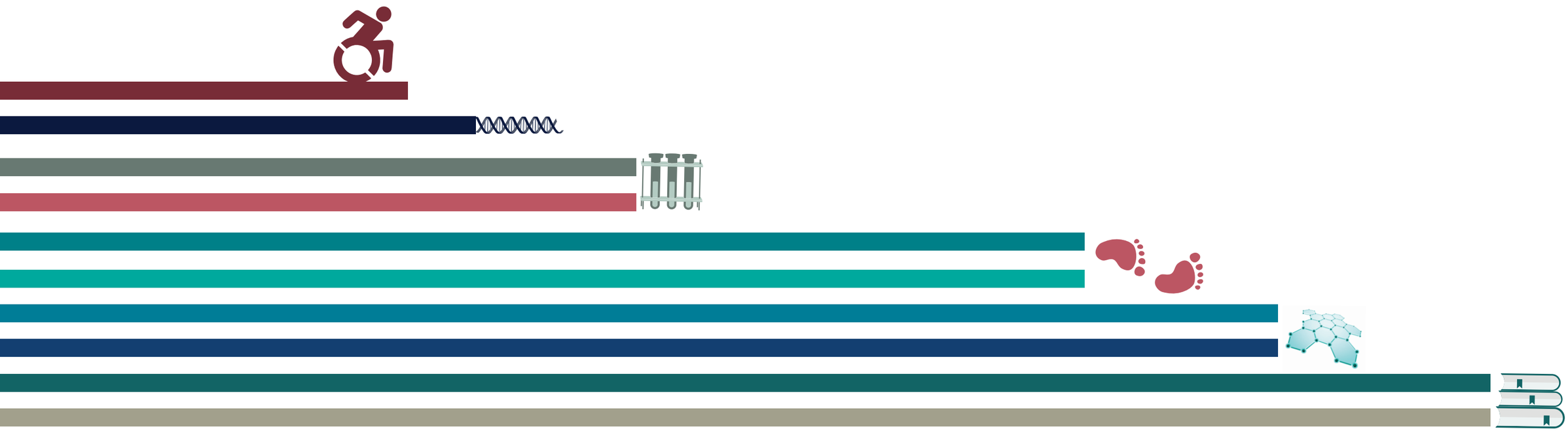
And say, Do [as you will], for Allah will see your deeds, and [so, will] His Messenger and the believers.

Surah At-Tawbah [9:105]

Scientific Report 2018

Science Benefiting People

Advanced Research Programs



Predictors of Physical Activity Limitation in Community-Dwelling Older Australian Men

Background/Objectives: As the numbers of the elderly has been increasing with the associated increase in both disability and health care, the need to identify the possible risk factors correlated with activity limitation, particularly, has become essential. Therefore, we conducted this current work to investigate such relationship.

Design:

This is a prospective cohort study of the Concord Health and Ageing in Men Project (CHAMP). Setting: Sydney, Australia. Participants: From the period of January 2005- June 2007, a total of 2815 men aged 70 years or older were contacted for participations and 194 joined through recruitment media. Men who were living in aged-care facilities were excluded. Participants were followed up for 2 years. Measurements:

A total of 24 independent variables were used in the univariate analysis and significant factors were included in the multivariate analysis.

Results

A total of 1367 participants completed the study. The majority were 75 years or younger (46.2%); socially-active (59.8%); with normal cognitive function (87.5%). Activity limitation was encountered in 91.6%, 31.4%, and 32.9% according to Katz score, 5-times chair stands and walking speed, respectively. The multivariate analysis revealed that age, educational level, polypharmacy, walking speed, cognitive function, and physical self-reported health status were significantly correlated with activity limitation according to Katz score. On the other hand, age at baseline, drug burden index, walking speed, grip strength, and physical health status were significantly correlated with 5-times chair stands (P <0.1). Whereas, walking speed at two years follow up was significantly correlated with baseline age, polypharmacy, frequency of falls, spoken language, and physical and mental health status (P <0.1).

Conclusion:

Age and physical self-reported health status are significant risk factors of activity limitation at all three outcome measures. Further work is warranted to identify more risk factors of independence, functional disability, and activity limitation in particular.

Keywords:

men; elderly; activity limitation; disability

Primary Investigator:

Ahmed Alhabter

Publication:

Awaiting response from the Journal of the American Geriatrics Society (JAGS). If not accepted, I will submit it to the Australasian Journal on Ageing (AJA)

Univariate for baseline and 2 yrs (all outcome variables)

Variable	Subgroup	Katz				5 times chair stands				Walking speed			
		Baseline		2 years follow up		Baseline		2 years follow up		Baseline		2 years follow up	
		Standardized coefficients (β)	*P value*	*Standardized coefficients (β)*	*P value*	*Standardized coefficients (β)*	*P value*	*Standardized coefficients (β)*	*P value*	*Standardized coefficients (β)*	*P value*	*Standardized coefficients (β)*	*P value*
Age		1.12	<0.001	1.14	**<0.001**	1.12	<0.001	1.1	**<0.001**	-0.32	<0.001	-0.14	**0.001**
Lives alone (Y/N)		1.07	0.77	1.18	0.52	1.41	0.009	0.37	0.83	-0.06	0.02	0	0.5
Number of comorbidities										-0.15	<0.001	-0.1	**0.009**
	None	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference				
	4 or less	2	0.12	2.85	**0.04**	2.56	<0.001	1.66	**0.05**				
	More than 4	5.57	<0.001	6.28	**0.001**	5.83	<0.001	2.06	**0.03**				
Currently married (Y/N)		0.91	0.63	1	0.97	1.3	0.03	1.01	0.94	0.08	0.002	0.04	0.18
Social interaction (high/low)		2.67	<0.001	1.65	**0.02**	1.78	<0.001	1.4	**0.03**	0.16	<0.001	0.07	**0.05**
Satisfaction with social support (high/low)		2.36	<0.001	1.75	**0.01**	1.8	<0.001	1.14	0.5	0.09	<0.001	0.04	0.19
Level of education										0.18	<0.001	0.04	0.15
	Post school education	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference				
	Did not go to school	1.71	0.48	2.92	0.17	1.02	0.97	0.49	0.5				
	Went to school	1.93	<0.001	2.06	**0.001**	1.39	0.002	1.71	**<0.001**				
Smoking										-0.04	0.06	-0.09	**0.02**
	Never	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference				
	Ex-smoker	1.22	0.3	1.2	0.39	1.11	0.33	1.12	0.49				
	Current	0.66	0.34	1	1	1.24	0.34	2.07	**0.02**				

A Comprehensive Molecular Research Program for Hereditary Channelopathies in the Kingdom of Saudi Arabia

Genetic Duct disorder is a heterogeneous group of disabilities and disorders caused by various electrical voltage or ion ducts. There are no statistics available on the number of people with this group of diseases, which hinders the verification of real rates of infection with Genetic Duct disorder in Saudi Arabia. It is expected that the rate would be high as Genetic Duct disorder includes diseases of nervous system, endocrine system, heart diseases, blood vessels, immune system, respiratory apparatus, and urinary system, which represents financial burden on health system.

The comprehensive program for detection and early diagnosis of these diseases provides greater effectiveness of therapeutic intervention and therefore reflected positively on the health, social and economic aspects. Researchers are working to take advantage of modern techniques for genetic studies such as next generation sequencing techniques, and Holistic molecular approach in order to determine new genetic genes and mutations for the diseases of Genetic Duct disorder. Besides Visualization of gene interaction networks, pathways related to these diseases and their pathobiology, and finally developing a comprehensive gene panel that will be used-Allah's will- for diagnosis, carrier testing, prenatal diagnosis and pre-implantation diagnosis.

Research's objectives:

- To collect biological samples from families having patients affected with HCPs in Saudi Arabia and perform clinical analysis of the patients.
- To determine genetic factors (mutations in known genes as well as novel genes) leading to the diseases in the patients (The priority will be given to AR channelopathies, but other mode of inheritance will not be excluded from the study).
- To establish a comprehensive database, create an up to date gene panel for rapid screening of patients and likely carriers for the CP mutations for diagnostics throughout KSA, and facilitate prenatal diagnosis and preimplantation genetic diagnosis for interested families and relatives.
- To create a comprehensive up-to-date HCP gene panel for rapid screening and diagnosis of the patients
- To study channelopathies related gene interaction networks and pathways using holistic integrative genomic analyses based on genomic variants, mRNA, and miRNA profiles from the patients and age/sex matching controls by means of next-generation sequencing techniques.

Achievements of 2018

- The recruitment and training of laboratory technicians on the devices and practical aspects of molecular experiments has been completed.
- Starting to select patients and families participating in the study in coordination with the concerned clinics.
- Checking for infected people who have genetic mutations in NALCN, GLRB and KCNA4 (schedule 1)
- The research team initiated molecular studies to characterize and determine the functional consequences of these mutations in cellular and human models.
- Initiating basic genetic analysis of patients and their families, including genome studies, axomial sequences, and target Inherited genes
- Initial results showed new mutations in Saudi patients and included the following genes KCTD7,KCNT1, SLC1A2 and KCNQ2 (schedule 2)
- A new genotype has been identified in a membrane canals, which may be a new syndrome of duct ailments.
- Starting the establishment of database of these families, clinical features, pathogenic genes, and types of potential mutations.

Gene	Chr	Mutation	Phenotype	NAI	IM
NALCN	13q33.1	p.W1287L	Hypotonia, DD	6	AR
GLRB	4q31.3	p.M177R	Hyperekplexia	13	AR
KCNA4	11p14.1	p.R89Q	Cataract, DD	4	AR

AR: Autosomal recessive, DD: Developmental Delay, IM: Inheritance Mode, NAI: Number of Affected Individual, Ref: References

Table 1. HCP related genes and mutations discovered at Neurogenetics/Cognitive Genetics Unit (Dr. Kaya Lab) at KFSHRC. Two of these genes are first time mentioned in the literature through the work.

Gene	Chr	Refer	cDNA	Protein	Status
KCTD7	7q11.21	NM_153033	c.835C>T	p.R278C	Ongoing Work
KCNT1	9q34.3	NM_020822	c.2849G>A	p.R950Q	Ongoing Work
SLC1A2	11p13	NM_004171	c.1466G>C	p.G489A	Ongoing Work
KCNQ2	20q13.33	NM_004518	c.1042G>A	p.A348T	Ongoing Work

Table 2. HCP related genes and mutations discovered at Neurogenetics/Cognitive Genetics Unit (Dr. Kaya Lab) at KFSHRC during the progress period.

Expected objectives:

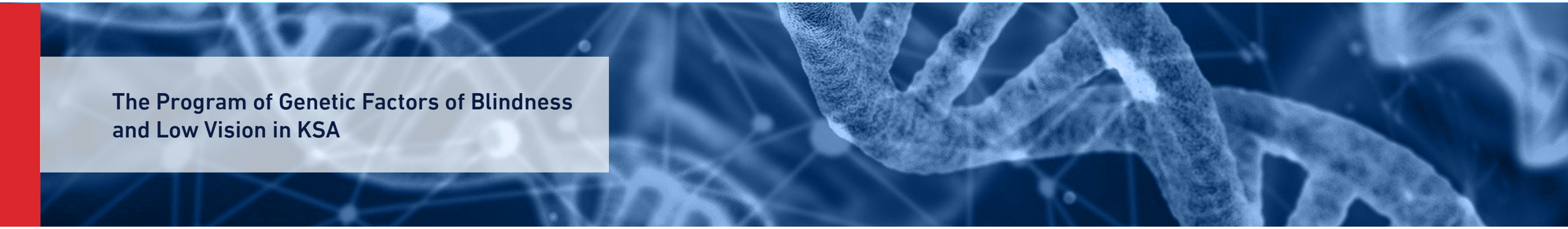
The research team will add more patients and their families in coordination with the relevant clinics and continue to work according to the objectives and plan of the project. The research team will prepare scientific papers for publication in specialized scientific journals.

PUBLICATIONS

1. Kaya N*, Alhassnan Z, Abdulrahim M, Aldosary M, Colak D "Hereditary Disorders and Human Mutations of Iron-Sulfur Assembly Genes", in Mitochondrial Disease, ISBN 978-953-51-5566-9Book edited by: Dr. Eylem Taskin, Dr. Celal Guven, Dr. Yusuf Sevgiler 2018, DOI: 10.5772/intechopen.78006, InTech Open Access Publisher.

2. Chelban V, Kaya N, Alkuraya FS, and Houlden H NKX6-2 Disorder. GeneReviews, NCBI; In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. 2018 Oct 4 .PMID: 30285346

3. Alhassnan Z, Albawardi W, Almutairi F, AlMass R, Albakheet A, Mustafa OM, AlQuait L, Shinwari MA, Wakil S, Salih MA, Al-Fayyadh M, Hassan SM, Aljoufan M, AlNakhli O, Levy B, AlMaarik B, Al-Hakami HA, Alsagob M, Colak D, Kaya N*. Identification of novel genomic imbalances in Saudi patients with congenital heart disease. Mol Cytogenet. 2018 Jan 25;11:9. doi: 10.1186/s13039-018-0356-6. eCollection 2018.



The Program of Genetic Factors of Blindness and Low Vision in KSA

The genetic factors contribute with 70% of the loss of vision and low vision cases in Saudi children. Majority of vision loss in Saudi Arabia is likely to follow a monogenic, specifically autosomal recessive form of inheritance. This is attributed to high rates of inbreeding and consanguinity. Given this fact, primary prevention is the most effective method to combat genetic eye disorders. Such preventive methods include, the use of prenatal and preimplantation genetic diagnosis which cannot be offered without prior knowledge of the molecular defect that underlies the genetic eye condition being screened for.

Project Aim(s)

- To identify the genetic lesions (mutations) that underlies the various genetic forms of vision loss in the Saudi population.
- To establish a database of these mutations in order to facilitate the implementation of prenatal and preimplantation diagnosis.

Achievements During 2018:

Across the years, this project has contributed to the era of human genetics through the discovery of many novel gene mutations – disease causing among our population. Below are some of the accomplishments achieved in 2018.

1. ARL3 Mutations Cause Joubert Syndrome by Disrupting Ciliary Protein Composition.

Joubert syndrome (JBTS) is a genetically heterogeneous autosomal-recessive neurodevelopmental ciliopathy.

This study further investigated the underlying genetic etiology of Joubert syndrome by studying two unrelated families in whom JBTS was not associated with pathogenic variants in known JBTS-associated genes.

The main finding of this project includes

- Identification of ARL3 as a novel gene for Joubert syndrome in a Saudi family with classical eye and brain findings.
- Through an international collaboration, a second family was identified with a different mutation in this novel gene.
- The work showed that the encoded protein, ADP ribosylation factor-like GTPase 3 (ARL3), is a small GTP-binding protein that is involved in directing lipid-modified proteins into the cilium in a GTP-dependent manner.
- Both missense variants replace the highly conserved Arg149 residue, which showed to be necessary for the interaction with its guanine nucleotide exchange factor ARL13B, such that the mutant protein is associated with reduced INPP5E and NPHP3 localization in cilia.

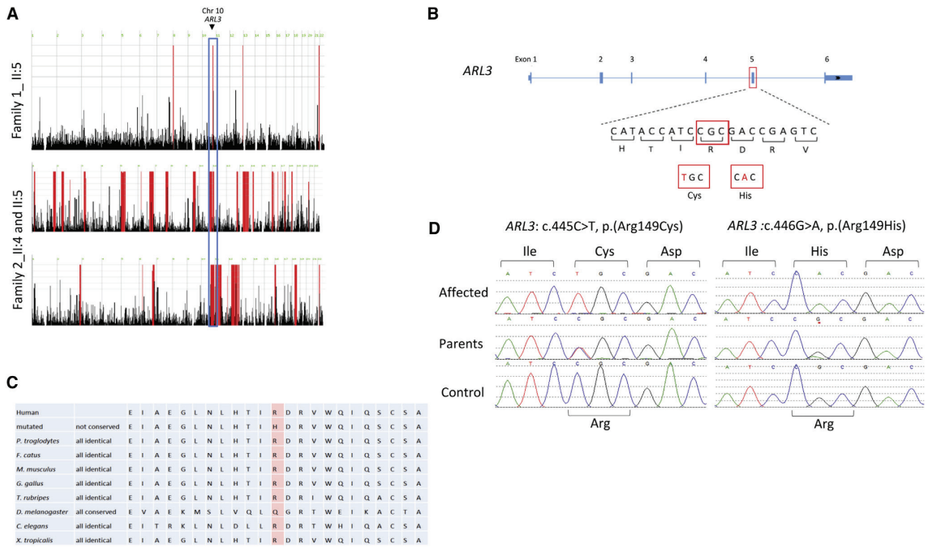


Figure: Molecular Genetic Investigations of the Two JBTS-Affected Families.

(**A)** Genome-wide homozygosity mapping shows the shared homozygous region between the affected members of the two families on chromosome 10 (blue rectangle). **(B)** Schematic representation to ARL3 with the homozygous missense variants located in exon 5. **(C)** Evolutionary conservation of residue Arg149, which is highly conserved throughout all species shown except D. **(D)** Sequence chromatograms of the two different ARL3 variants described in this study.

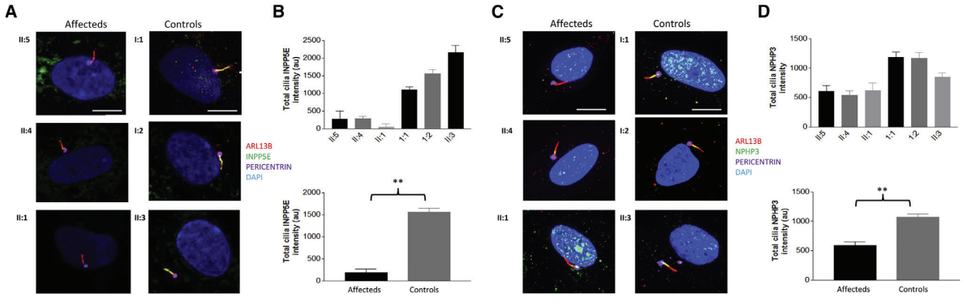


Figure: Characterization of Ciliary Phenotype in ARL3-Mutant Fibroblasts from Family 2.
(A and C) Affected and control fibroblasts were observed under high-power immunofluorescence for determining ciliary expression of (A) INPP5E and (C) NPHP3. **(B)** Quantification of ciliary localization of INPP5E (**p < 0.0001, unpaired t test, n > 150 cilia for each group). **(D)** Quantification of ciliary localization of NPHP3 (**p < 0.0001, unpaired t test, n > 150 cilia for each group).

This study was published in the prestigious journal American Journal of Human Genetics

ARL3 mutations cause Joubert syndrome by disrupting ciliary protein composition. Alkanderi S, Molinari E, Shaheen R, Elmaghloob Y, Stephen LA, Sammut V, Ramsbottom SA, Srivastava S, Cairns G, Edwards N, Rice SJ, Ewida N, Alhashem A, White K, Miles CG, Steel DH, Alkuraya FS, Ismail S, Sayer JA. Am J Hum Genet. 2018 Oct 4;103(4).PMID: 30269812.

2. Mutations in known disease genes account for the majority of autosomal recessive retinaldystrophies.

Retinal dystrophies (RDs) are hereditary blinding eye conditions that are highly variable in their clinical presentation. Until the recent advent of next-generation sequencing, the remarkable genetic heterogeneity that characterizes RD was a major challenge in establishing the molecular diagnosis in these patients. It remains unclear, what percentage of autosomal recessive RD remain undiagnosed when all established RD genes are sequenced. In this study, 75 new families with autosomal recessive retinal dystrophies were enrolled and accomplishment summary was provided.

The main finding of this project includes

- The yield of a multigene panel that contains known RD genes is 67.5%.
- The higher yield (82.3%) when whole exome sequencing was implemented instead was often due to hits in genes that were not included in the original design of the panel.
- Description of 45 unique likely deleterious variants (of which 18 are novel including one deep intronic and one genomic deletion mutation).

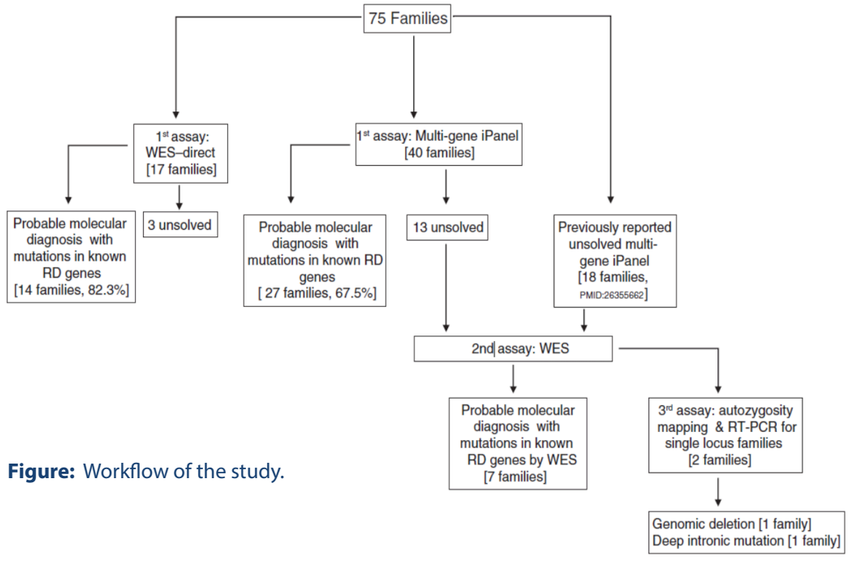


Figure: Workflow of the study.

This study was published in the prestigious journal American Journal of Clinical Genetics

Mutations in known disease genes account forthe majority of autosomal recessive retinaldystrophies. Patel N, Alkuraya H, Alzahrani SS, Nowailaty SR, Seidahmed MZ, Alhemidan A, Ben-Omran T, Ghazi NG, Al-Aqeel A, Al-Owain M, Alzaidan HI, Faqeih E, Kurdi W, Rahbeeni Z, Ibrahim N, Abdulwahab F, Hashem M, Shaheen R, Abouelhoda M, Monies D, Khan AO, Aldahmesh MA, Alkuraya FS. Clin Genet. 2018 Dec; 94(6):554-563. doi: 10.1111/cge. PMID:30054919.

3. Congenital glaucoma and CYP1B1: an old story revisited.

Primary congenital glaucoma is a trabecular meshwork dysgenesis with resultant increased intraocular pressure and ocular damage. CYP1B1 is the best-known gene for congenital glaucoma, a disease that is particularly common in our country due to a very high carrier frequency of a G61E founder mutation. However, many questions remained unanswered about CYP1B1-related congenital glaucoma. In this study, a modern genomic approach to re-examine CYP1B1-related congenital glaucoma was employed.

The main finding of this project includes:

- Identification of biallelic CYP1B1 mutations in 80.8% (87.5 and 66.1% in familial and sporadic cases, respectively, $p < 0.0086$) among a cohort of 193 patients (136 families) diagnosed with congenital glaucoma.
- With the exception of c.1103G>A (p.R368H), previously reported pathogenic mutations were highly penetrant (91.2%).
- The study concluded from the very low penetrance and genetic epidemiological analyses that c.1103G>A (p.R368H) is unlikely to be a disease-causing recessive mutation in congenital glaucoma as previously reported.
- All cases that lacked biallelic CYP1B1 mutations underwent whole exome sequencing. No mutations in LTBP2, MYOC or TEK were encountered.
- Mutations were identified in genes linked to other ophthalmic phenotypes, some inclusive of glaucoma, highlighting conditions that might phenotypically overlap with primary congenital glaucoma (SLC4A4, SLC4A11, CPAMD8, and KERA).
- The study encountered candidate causal variants in genes not previously linked to human diseases: BCO2, TULP2, and DGKQ.

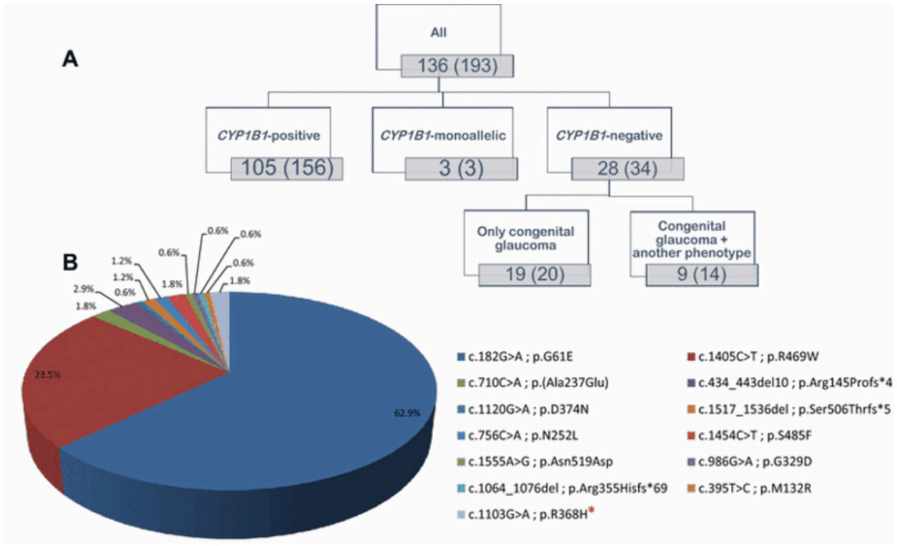


Figure: **(A)** Distribution of CYP1B1 mutations in the study cohort. Numbers denote families and numbers in parenthesis denote absolute counts of individuals. **(B)** Pie chart distribution of 13 mutations identified in CYP1B1

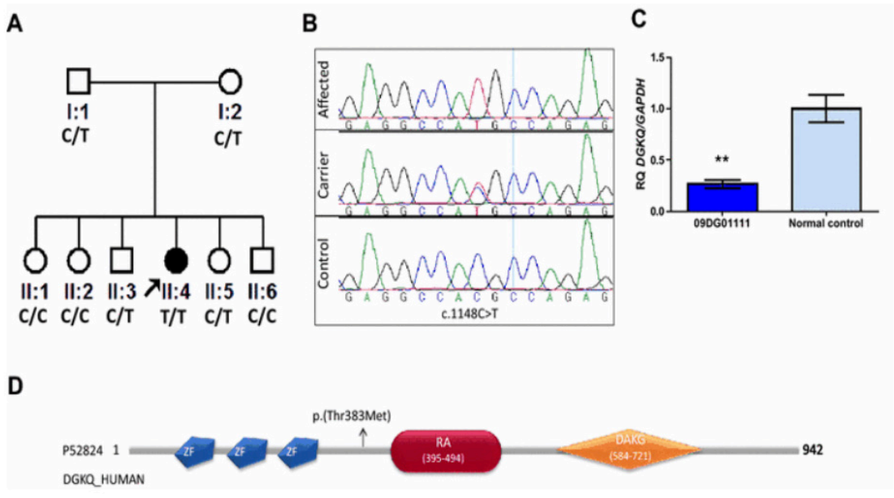


Figure: **(A)** Pedigree of the family with congenital glaucoma and a novel DGKQ variant. **(B)** Sequence chromatogram of the novel DGKQ variant. **(C)** qRT-PCR for DGKQ expression in LCL in patient 09DG01111 with a missense mutation in this candidate gene compared to three normal control reveals >70% decreased in expression.

This study was published in the prestigious journal American Journal of Human Genetics

Congenital Glaucoma and CYP1B1: An Old Story Revisited. Hessa S. Alsaif · Arif O. Khan· Nisha Patel · Hisham Alkuraya · Mais Hashem · Firdous Abdulwahab · Niema Ibrahim · Mohammed A. Aldahmesh · Fowzan S. Alkuraya. Hum Genet. 2018 Mar 19. doi: 10.1007/s00439-018-1878-z. PMID: 29556725.

4. Genetic investigation of 93 families with microphthalmia or posterior microphthalmos.

Microphthalmia is a developmental eye defect that is highly variable in severity and in its potential for systemic association. Despite the discovery of many disease genes in microphthalmia, at least 50% of patients remain undiagnosed genetically.

In this study we describe a cohort of 147 patients (93 families) from our highly consanguineous population with various forms of microphthalmia (including the distinct entity of posterior microphthalmos) that were investigated using a next-generation sequencing multi-gene panel (i-panel) as well as whole exome sequencing and molecular karyotyping.

The main finding of this project includes:

- A potentially causal mutation was identified in the majority of the cohort with microphthalmia (61%) and posterior microphthalmos (82%). The identified mutations (55 point mutations, 15 of which are novel) spanned 24 known disease genes, some of which have not or only very rarely been linked to microphthalmia (PAX6, SLC18A2, DSC3 and CNKSR1).

- Our study has also identified interesting novel candidate variants in 2 genes for microphthalmia that have not been linked to human diseases (MYO10 and ZNF219).

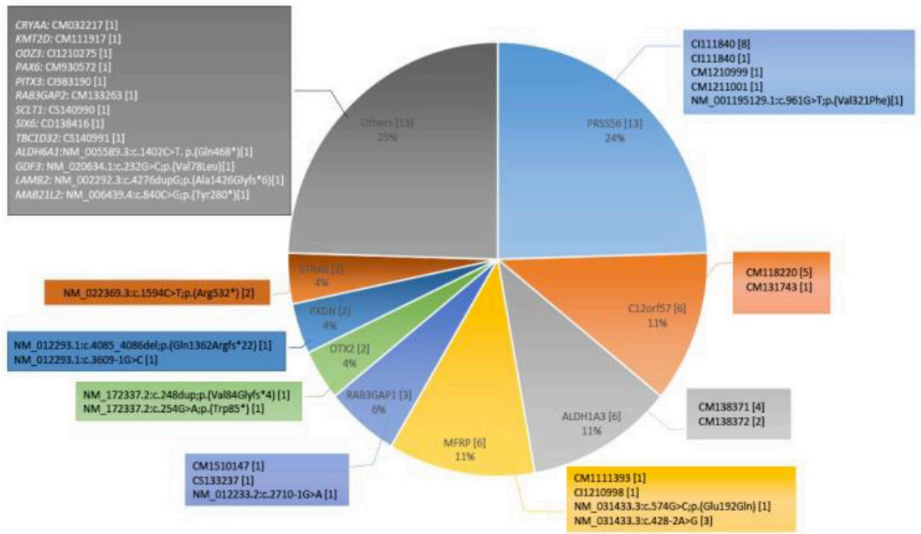


Figure: Pie chart illustrating the distribution of mutations across 21 disease causing genes known to cause microphthalmia. Numbers in square brackets indicate the occurrence of that particular mutation within the cohort. HGMD accession numbers are noted for previously reported mutations, while full HGVS nomenclature is given for novel mutations.

This study was published in the prestigious journal American Journal of clinical Genetics

Genetic investigation of 93 families with microphthalmia or posterior microphthalmos. Patel N, Khan AO, Alsahli S, Abdel-Salam G, Nowilaty SR, Mansour AM, Nabil A, Al-Owain M, Sogati S, Salih MA, Kamal AM, Alsharif H, Alsaif HS, Alzahrani SS, Abdulwahab F, Ibrahim N, Hashem M, Faquih T, Shah ZA, Abouelhoda M, Monies D, Dasouki M, Shaheen R, Wakil SM, Aldahmesh MA, Alkuraya FS. Clin Genet. 2018 Jun;93(6):1210-1222. doi: 10.1111/cge.13239. Epub 2018 Mar 25. PMID: 29450879.

The Genetic Description of Deafness-Hearing Impairment and Growth in KSA

Deafness is the most common sensory deficit in humans with both genetic and environmental etiologies. It is estimated that the incidence in Saudi Arabia is three times that of the worldwide rate. Hearing impairment is clinically and genetically heterogeneous. During the last decade, many deafness loci and the underlying genes have been identified at a rapid rate.

The major objectives of this study are:

- To conduct further collection (using IRB approved consent), clinical and genetic analysis of families affected by syndromic and non-syndromic hereditary deafness.
- Identifying the pathogenic mutation in the newly recruited families and in the remaining 150 families that have already been enrolled and DNA has been previously collected.
- The above two aims will be carried out using already established linkage analysis and homozygosity approaches in families with two or more affected individuals AND by using Next-Generation Sequencing technology to identify novel genes and for singleton cases where homozygosity mapping/linkage SNP-bases approaches are not amenable.
- To design, develop and validate a custom Hereditary Deafness Gene-Panel using Ion AmpliSeq™ Technology for rapid analysis of a large number of known genes causing hereditary deafness.

Achievements During 2018:

- Continued efforts to define the genetic basis of autosomal recessive deafness in the Saudi population took place, in where, additional 25 families comprising 128 cases in the project were enrolled. All these newly enrolled patients have been reviewed by the Genetics clinic at King Faisal Specialist Hospital and Research Center.
- Total number of cases enrolled in this project is 1011 patients/family members. Full clinical and family histories were recorded. Informed consent forms were taken and documented.
- Additional 23 mutations in 10 different genes were identified in these families. In total to date, 57 mutations in 24 different disease-causing genes from this cohort were identified.
-
- Preliminary validation on the deafness gene panel has been completed.
- The results of this work contributed to the inclusion of 57 genetic mutations within the genetic testing, carrier testing, and pre-marital diagnostic testing.
- The results of project were reported in two published manuscripts.
- ***Evidence for an autosomal recessive pattern of inheritance in Keratitis-ichthyosis-deafness (KID) syndrome: Exome sequencing reveals a novel homozygous GJB2 mutation. Khushnooda Ramzan, RozeenaHuma, Nouf S.Al-Numair, FaiqaImtiaz, MoeenaldeenAl-Sayed. Meta Gene Volume 19, February 2019, Pages 15-22.***
- ***Utility of whole exome sequencing in the diagnosis of Usher syndrome: Report of novel compound heterozygous MYO7A mutations. Khushnooda Ramzana, Mohammed Al-Owainb, Rozeena Humab, Selwa A.F. Al-Hazzaa, Sarah Al-Ageele, Faiqa Imtiaza, Moeenaldeen Al-Sayedb. Int J Pediatr Otorhinolaryngol. 2018 May;108:17-21. doi: 10.1016/j.ijporl.2018.02.016. PMID: 29605349***

Future Directions for 2019:

In the future, more individuals from some families will be recruited in order to assist in narrowing and excluding some regions that will be helpful in identifying the disease-causing mutation. Additionally, the analysis on the current enrolled families will be completed. As well as continuing to be recruiting more families as per the goals of the approved aims. Similarly, the identification of disease-causing mutations in our patients will be accelerated by using the custom-made Deafness Gene Panel (Ion Torrent) and the previous approved methodologies.

It is anticipated to continue by extending the search for pathogenic mutations and identification of possible novel deafness-causing genes using Next-Generation Sequencing technology. This technology will be used in particular in those patients, in which mutations were excluded in known deafness causing genes.

Gene	Mutation	Amino acid change
MYO7A	c.2005C>T	**p.R669***
MYO7A	IVS1+5G>A (c.1+470G>A)	
MYO7A	c.3592_3591delCT	p.C1198Rfs*30
MYO7A	c.4503_4502delTG	p.V1501Gfs*2
MYO7A	c.5617C>T	p.R1873W
MYO7A	c.4818_4818delG	p.K1606Nfs*39
MYO7A	c.6230_6229 insG	p.K2078Efs*50
MYO7A	c.4818_4818delG	p.K1606Nfs*39
MYO7A	c.2489G>A	p.R830H
MYO7A	c.5617C>T	p.R1873W
MYO7A	c.3588_3586delCTT	p.F1963del
MYO7A	c.199_198insA	p.Val67Ser fs*73
MYO7A	c.1226_1219del	p.Phe407Cys fs*36
MYO7A*	c.3514T>A	Y1172N
MYO7A*	c.6062A>G	K2021R
MYO7A*	c.3592 T>C	p.C1198R
OTOF	IVS 1+39 G>T (c.1+4960G>T)	N/A
OTOF	c.5375G>A	p.R1792H
OTOF	c.1544T>C	I515T
SLC26A4	c.1253G>T	p.G418V
SLC26A4	c.1199_1197delT	p.C400Vfs*32
SLC26A4	IVS1+12 G>A	
SLC26A4	c.1198delT	p.C400VfsX32
TMC1	c.100C>T	p.R34*
TMC1	c.1714G>A	D572N
TMC1	c.758C>T	S253F
MYO15A	c.1047C>A	p.Y349*
MYO15A*	c.8552C>T	A2851V
MYO15A*	c.1+4655G>A(IVS1+14G>A)	
MYO15A*	c.4240G>A	p.E1414K
HGF	c.2083C>T	p.R695C
HOXA1	c.176_175insG	p.V59Gfs*119
LARS2	c.457A>C	p.N153H
LHX3	c.437G>T	p.C146F
LHX3	c.466C>T	p.R156*
CLDN14	c.191G>A	p.C64Y
PCDH15	c.4711C>T	p.Q1571*
PEX6	c.290T>G	p.V97G
ATP6V1B1	c.1424G>A	p.W475X
GJB2	35delG	N/A
CDH23	c.1052C>T	p.P351L
CDH23	c.5495G>A	p.G1832E
CDH23*	c.3608A>T	D1203V
CDH23*	c.6367G>A	G2123R
CDH23*	c.6629 C>T	p.P2210L
GIPC3	c.122C>A	p.T41K
ILDR1	c.333_325dupAATGAGCCC	p.Asn109_Pro111dup
PJVK	c.818dupT	p.L273fs
PTPRQ	c.1+4093 G>A	
SLC29A3	c.243del A	p.k81NfsX20
MYO6	c.1607C>G	p.P536R
SCARF2	c.773G>A	p.C258Y
USH2A*	IVS1-3 G>C	
USH2A*	c.1-486 G>C	

Gene	Mutation	Amino acid change
PEX6	c.290T>G	p.V97G
OTOA*	c.2+398 T>A	
OTOA*	c.2204A>G	p.Y735C

Table: describe the disease-causing mutation in each specific gene: in patients with hereditary deafness from different families that are enrolled in this study. The rows written in red indicates the mutations identified in the current progress report year. The mutation with the sign (*) are identified first time in this study.

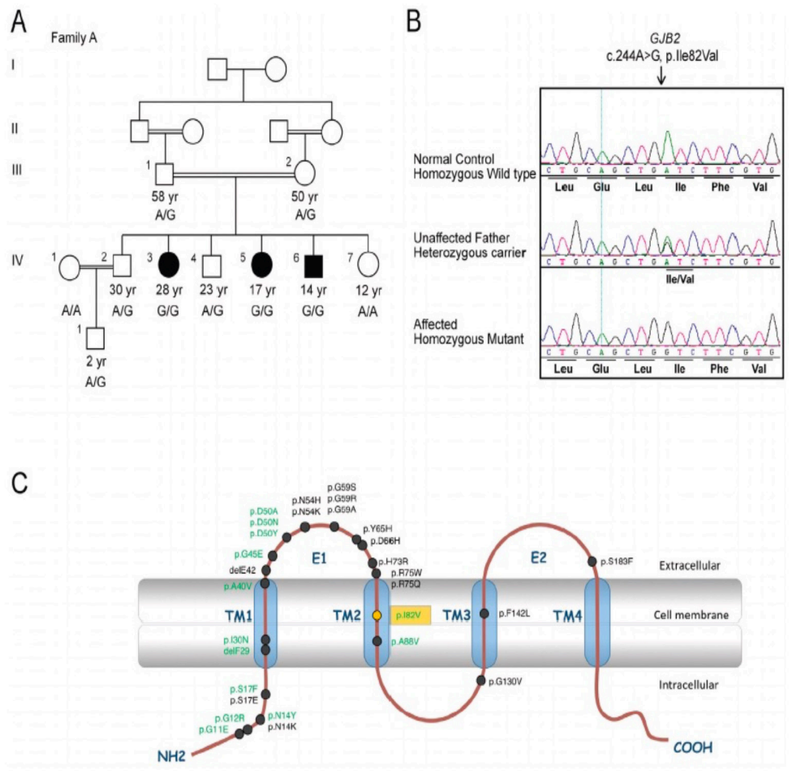


Figure: (A) Pedigree and the genotypes of family members with autosomal recessive KID syndrome. (B) GJB2 Sequence chromatograms of normal control. (C) Connexin 26 mutations causative for several syndromic forms of hearing loss associated to skin problems.

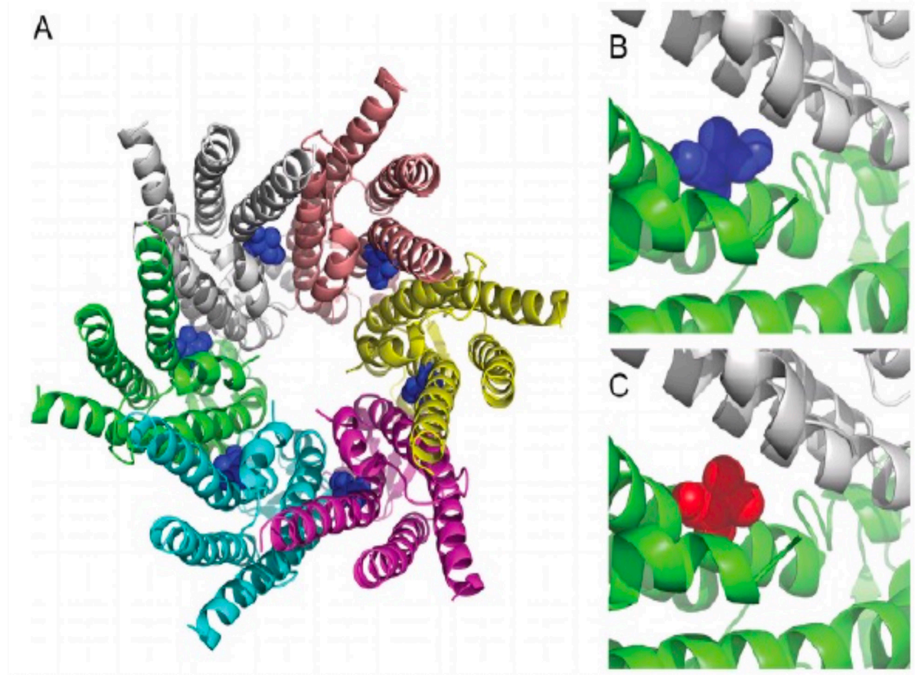


Figure: (A) The Connexin (6 subunits) and the oligomerization pattern of Cx26 hexameric chains are depicted. (B and C) show the structures of the wild-type residue.

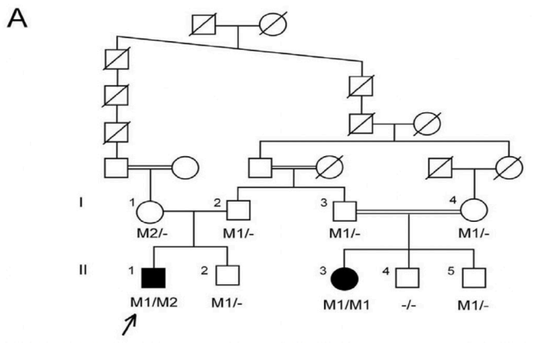


Figure: (A) Pedigree of the family showing the segregation of MYO7A mutations with Usher syndrome.

B

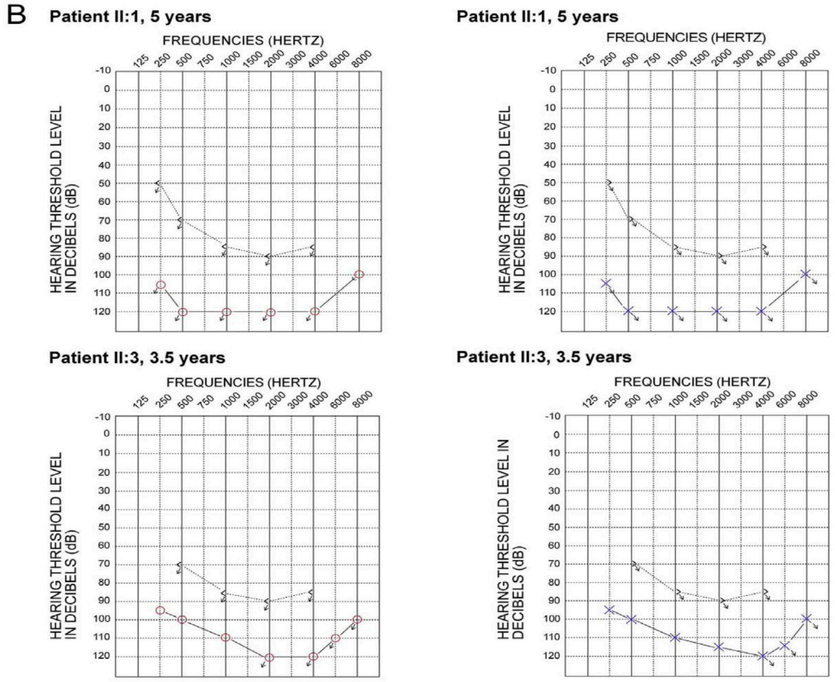


Figure: (B) Representative pure-tone air and bone conduction audiometric results of Patients II:1 and II:3.

C

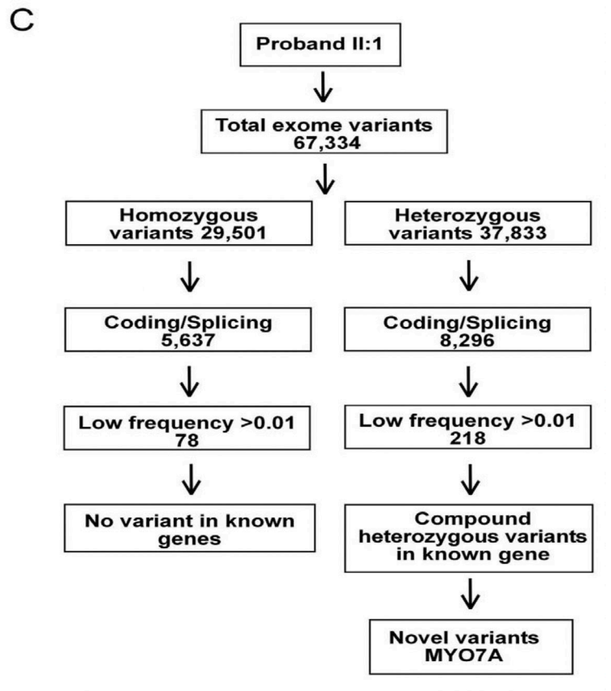


Figure: (C) Novel variants in MYO7A were detected as the only possibly causative variants.

D

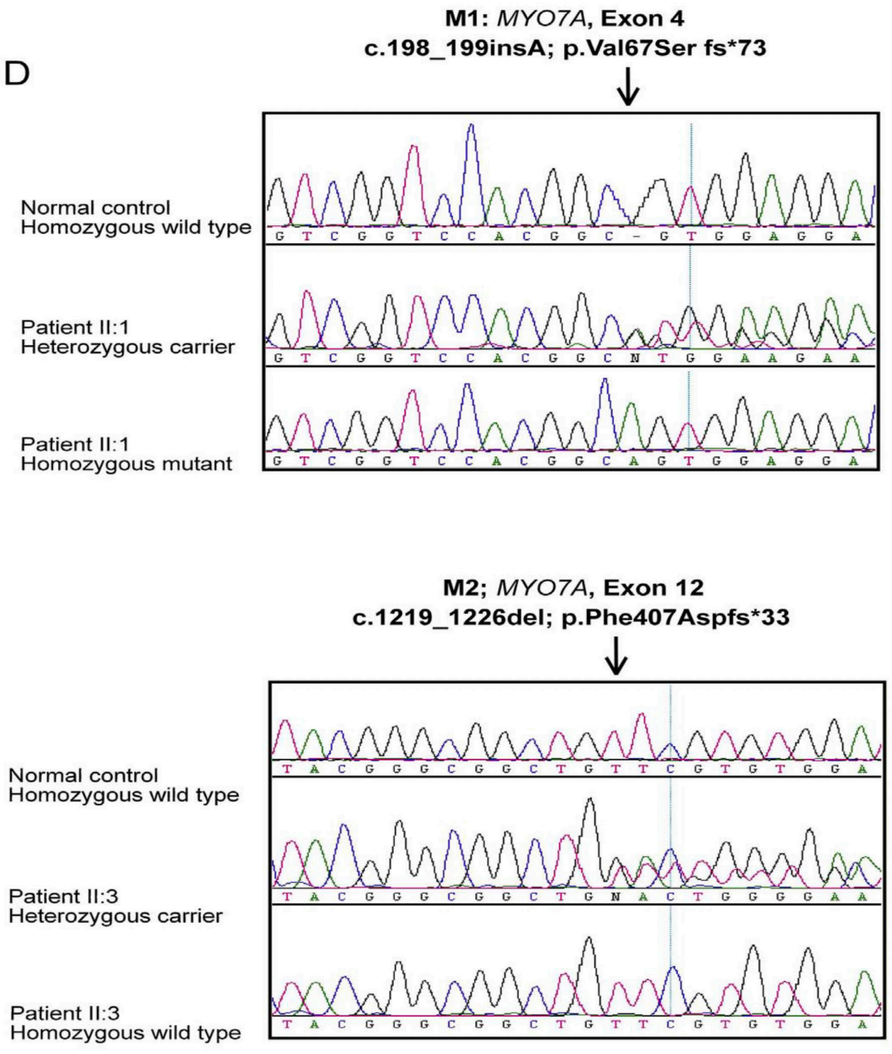


Figure: (D) Electropherograms showing the Sanger sequencing confirmation of the mutations identified in the proband by CES. **(E)** A full-length wild type myosin-VII A protein structure.

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