مركز الملك سلمان لأبحاث الإعاقة
King Salman Center For Disability Research
Science Benefiting People
علم ينفع الناس

Scientific Report 2018

Science Benefiting People

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]

King Salman Center for Disability Research

The United Nations convention on the Rights of Persons with Disabilities (UNCRPD) defines disability as "an evolving concept", but also stresses that "disability results from the interaction between persons with impairments and attitudinal and environmental barriers that hinder their full and effective participation in society on an equal basis with others". It is estimated that 15% of the world's populations - some 785 million people - has a significant physical or mental disability, including about 5 percent of children (2011 World Report on Disability – a report prepared jointly by the World Health Organization and the World Bank).

Research is essential for increasing public understanding about disability issues, informing disability policy and programs, and efficiently allocating resources. The World Report on Disability made specific recommendations on several areas for research on disability including:

- the impact of environmental factors (policies, physical environment, attitudes) on disability and how to measure it;
- the quality of life and well-being of people with disabilities;
- barriers to mainstream and specific services, and what works in overcoming them in different contexts;
- accessibility and universal design programs appropriate for low-income settings;
- the interactions among environmental factors, health conditions, and disability – and between disability and poverty;
- the cost of disability and the cost–effectiveness of public spending on disability programs.

The leadership in the Kingdom of Saudi Arabia realized the social and economic burden of disability in society and in 1993 moved forward to address this issue through the establishment of the King Salman Center for Disability Research (KSCDR) , a non-profit research organization that is governed by the KSCDR Board of Directors and motivated by the belief that persons with disabilities have the right to a better quality of life and should be provided every opportunity afforded to persons without disabilities. KSCDR firmly believed that research is a powerful tool that will help achieve a better quality of life. "Knowledge that benefits mankind" is actioned by sponsoring, coordinating and funding research and academic activities that is directed at solving medical, physical, psychological, educational, or social difficulties that face persons with disabilities which ultimately will be beneficial to Saudi society specifically, and humanity in general.



2018

Scientific Report

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Scientific Reports

A novel ISLR-2linked autosomal recessive syndrome of congenital hydrocephalus, arthrogryposis and abdominal distension

Congenital hydrocephalus is an important birth defect of brain development. The combination of congenital hydrocephalus and arthrogryposis has only rarely been reported. In this article a description of a multiplex consanguineous family in which a homozygous truncating variant in ISLR2 segregates with severe congenital hydrocephalus, arthrogryposis multiplex congenita and abdominal distension is represented.

The main finding of this project includes:

- Two novel (absent in gnome AD and a local database of ~2300 exomes) homozygous variants within the candidate autozygome fully segregated with the disease in the family: a missense (PCDH9: NM_020403.4:c.652T>C:p.(Tyr218His) and a frameshift deletion (ISLR2NM_020851.2:c.1660delT:p.(Trp554Glyfs*40).

- The phenotype of Islr2−/− (severe congenital hydrocephalus) and the truncating nature of the mutation argue strongly in favor of ISLR2 as the gene underlying this syndrome.

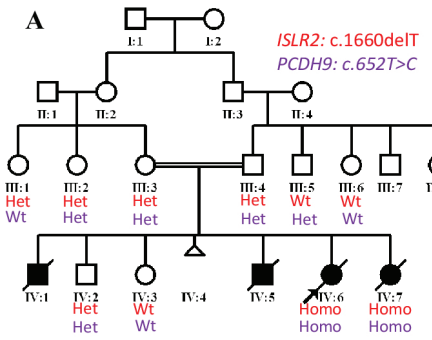


Figure (A) Pedigree of the family and their genotypes for both variants in ISLR2 and PCDH9.

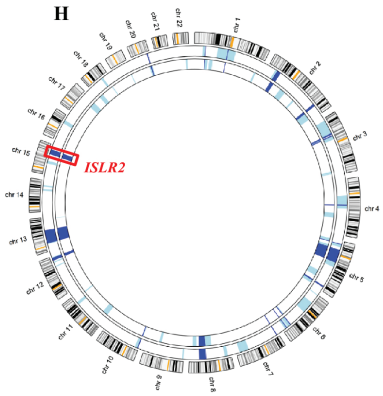
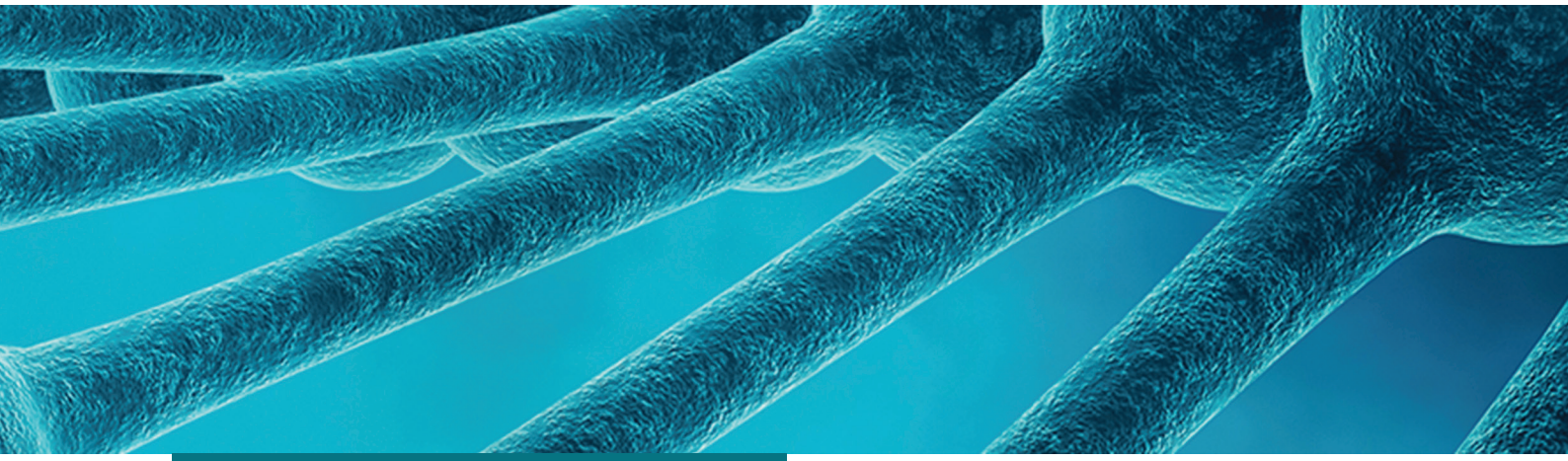


Figure (H) Circular ideogram of the available affected members' genome.



Conclusion & Future Directions:

Arthrogryposis is not described in Islr2–/– mouse models, nor are abnormalities of the gastrointestinal system so it remains to be seen if the progressive abdominal distension observed in the study family is recapitulated by these models. Future families with different biallelic variants in ISLR2 will be required to confirm the proposed link to the syndrome we describe here, and to delineate its full phenotypic spectrum.

This study was published in the prestigious journal

American Journal of Human Genetics

A novel ISLR2-linked autosomal recessive syndrome of congenital hydrocephalus, arthrogryposis and abdominal distension. Alazami AM1, Maddirevula S1, Seidahmed MZ2, Albhlal LA3, Alkuraya FS4,5. Hum Genet. 2018 Nov 27. doi: 10.1007. PMID:30483960.

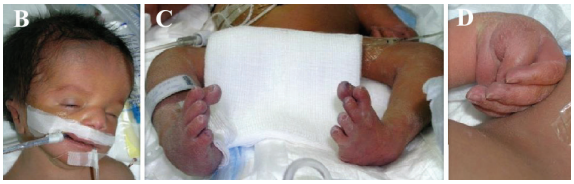


Figure (B-D) Clinical images of the index.

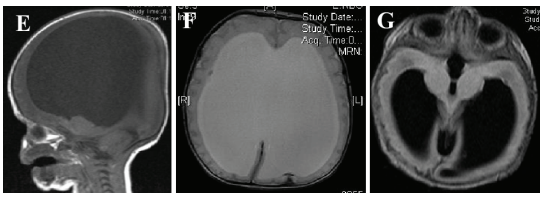


Figure (E-G) MRI images showing hydrocephalus.

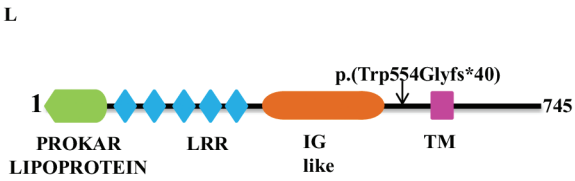


Figure (L) ISLR2 protein structure showing the mutation and functional domains.

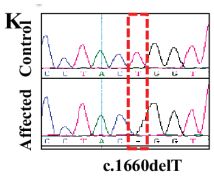


Figure (K) Sequencechromatogram showing deletion of T.

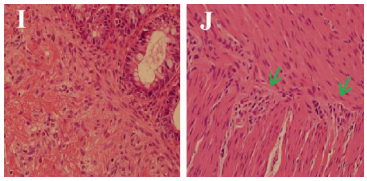
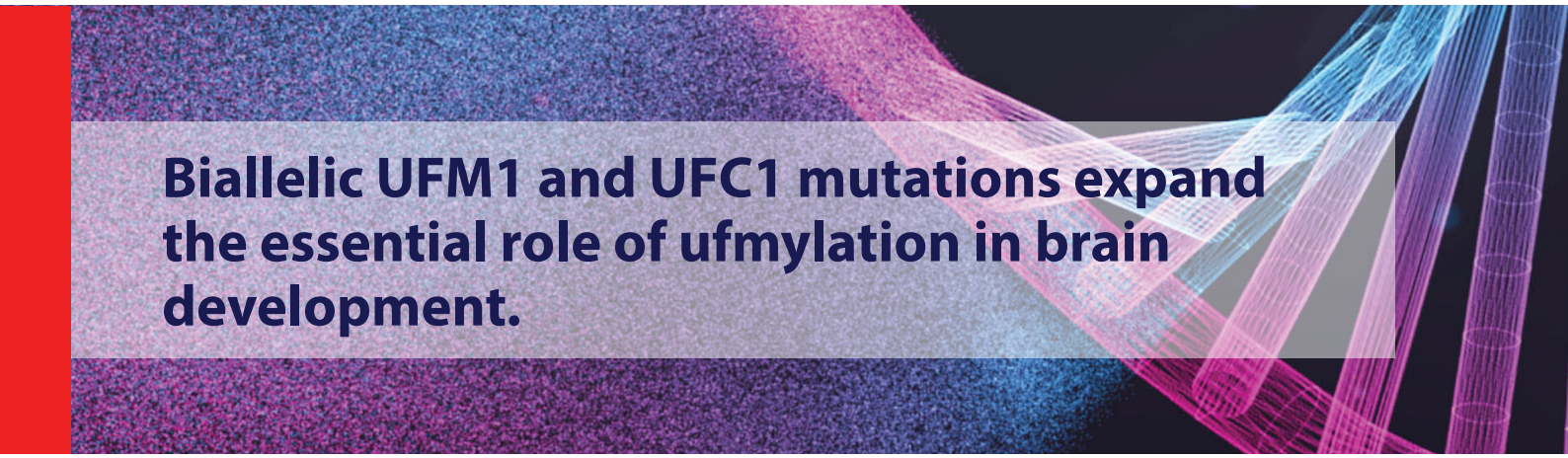


Figure (I-J) Rectal biopsy.



Biallelic UFM1 and UFC1 mutations expand the essential role of ufmylation in brain development.

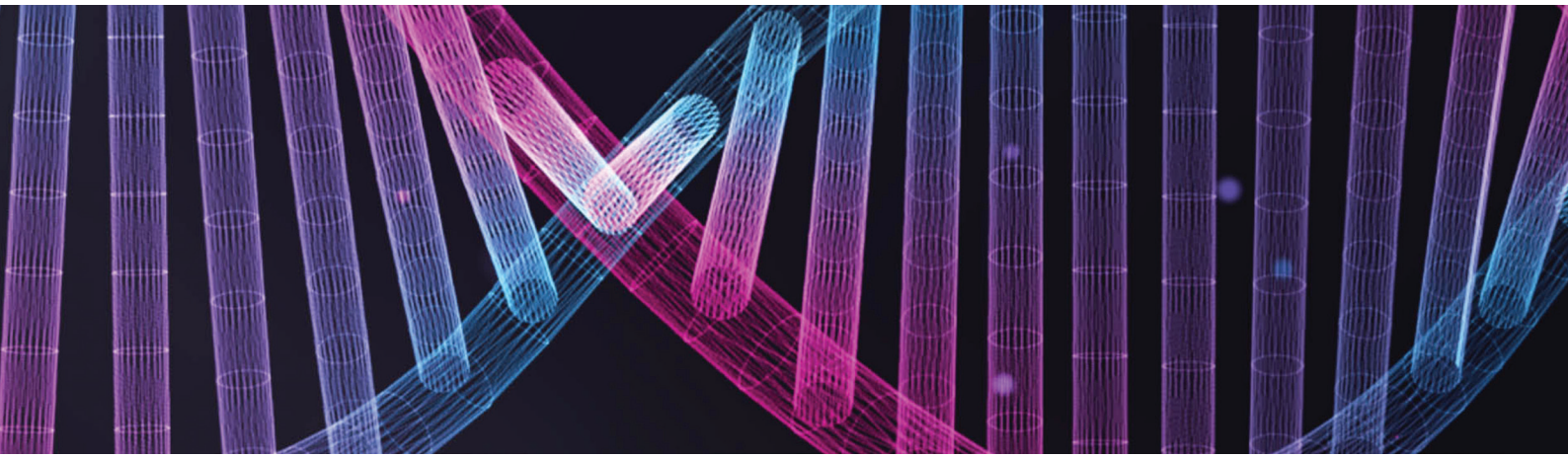
The post-translational modification of proteins through the addition of UFM1, also known as ufmylation, plays a critical developmental role as revealed by studies in animal models. More recently, a homozygous UFM1 variant was proposed as candidate etiology of severe early-onset encephalopathy with progressive microcephaly. This study involves the establishment of a locus for severe early-onset encephalopathy with progressive microcephaly based on two families, and maps the phenotype to a novel homozygous UFM1mutation.

The main finding of this project includes:

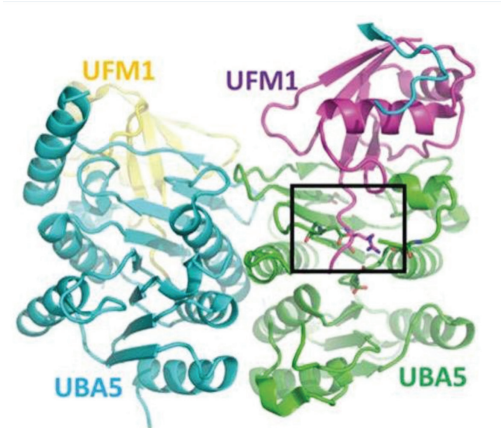
- Identification of two novel forms of severe global developmental delay with cortical blindness and were able to link them both to the ufmylation pathway. Specifically, a novel missense variant in UFM1 in one family and were able to identify another family from the UK with the exact same variant.
- Identification of other four Saudi families with a very similar phenotype who all shared the same founder variant in UFC1 (the E2-like enzyme for ufmylation) with resulting impaired ufmylation of cellular proteins.

Conclusion & Future Directions:

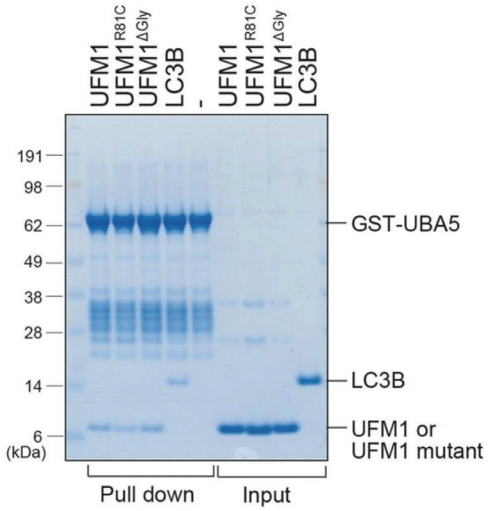
In conclusion, the remarkable resemblance between UFM1- and UFC1-related clinical phenotype and biochemical derangements strongly argues for an essential role for ufmylation in human brain development. The study suggests that impaired ufmylation leads to a recognizable syndrome of severe infantile encephalopathy and progressive microcephaly with or without epilepsy. Further studies are needed to discern the exact pathomechanism of ufmylation-related neurodevelopmental disorder, which may lead to possible therapies especially when one considers the hypomorphic nature of the observed mutations.



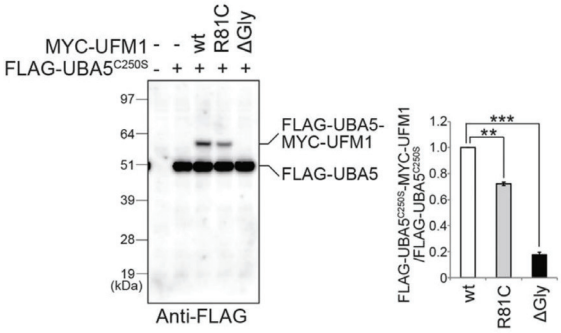
Hypomorphic effect of the UFM1 mutation on the UFM system

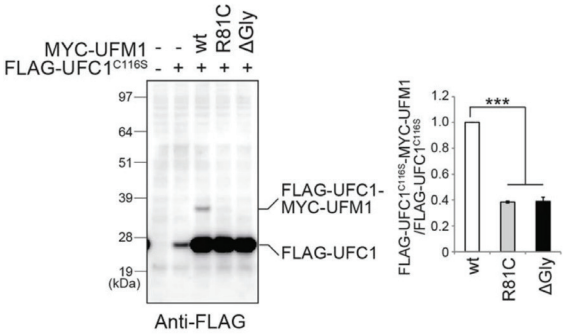


Molecular basis for the effect of the UFM1R81C mutation.

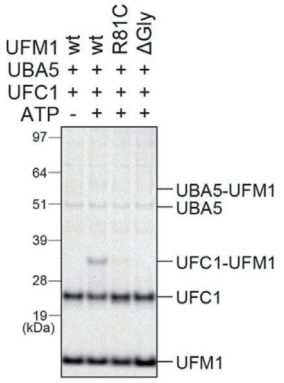


In vitro pull-down assay. Pull-down assay with GST-UBA5 and UFM1, UFM1 mutants or LC3B.

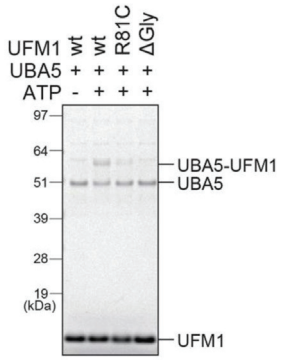




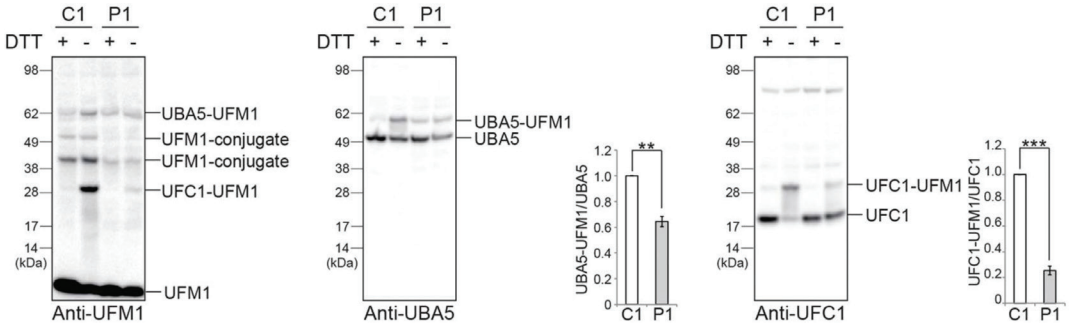
Immunoblot assay.



In vitrothioester formation assay of UFM1 by UBA5



In vitrothioester formation assay of UFM1 by UFC1



Hypomorphic effect of UFC1 mutants on the UFM system.

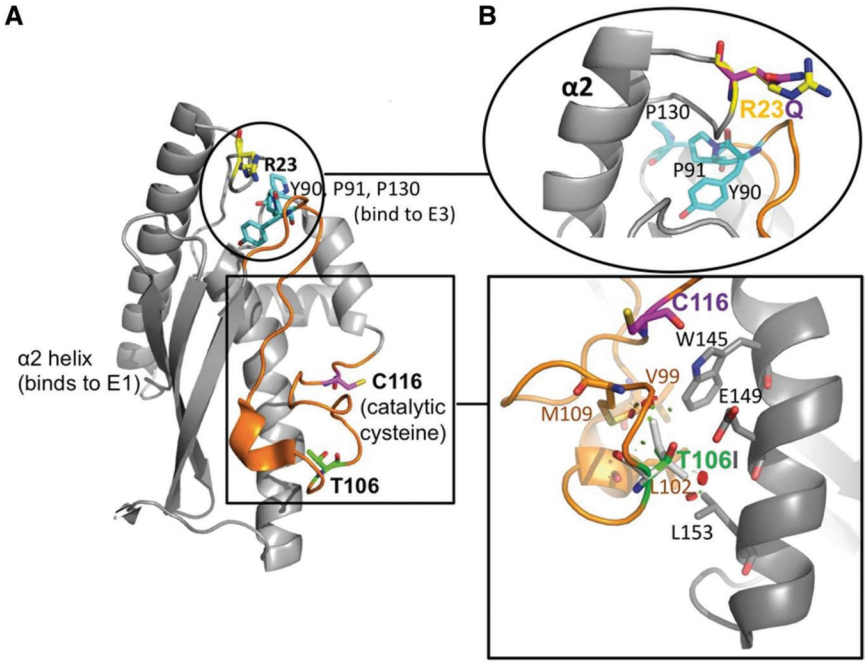


Figure (A) Localization of the key binding sites on UFC1. Binding sites for E1 and E3 are indicated. **Figure (B)** Bottom: Magnification of Thr106.

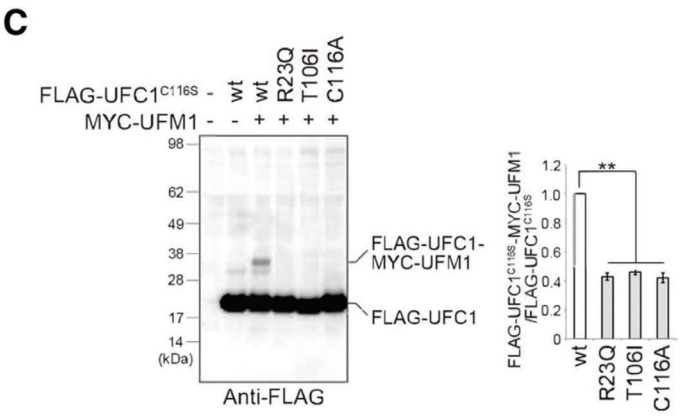


Figure (C) Immunoblot assay.

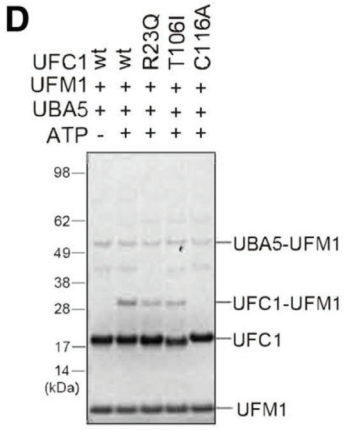


Figure (D) In vitro thioester formation assay of UFM1 by UFC1.

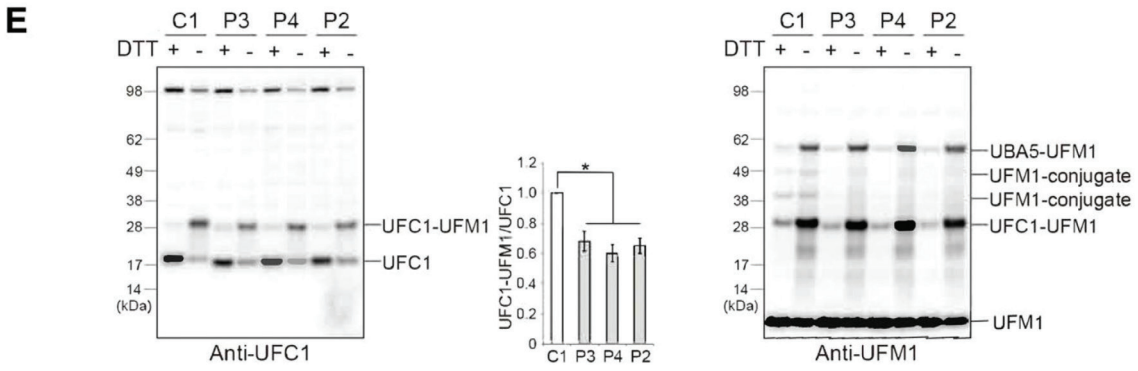


Figure (E) Immunoblot analysis in case (P2, P3, P4: V:1) and control (C1: a healthy Sudanese young females) lymphoblasts.

This work has been published in the prestigious journal Brain.

Biallelic UFM1 and UFC1 mutations expand the essential role of ufmylation in brain development.

Nahorski MS, Maddirevula S, Ishimura R, Alsahli S, Brady AF, Begemann A, Mizushima T, Guzmán-Vega FJ, Obata M, Ichimura Y, Alsaif HS, Anazi S, Ibrahim N, Abdulwahab F, Hashem M, Monies D, Abouelhoda M, Meyer BF, Alfadhel M, Eyaid W, Zweier M, Steindl K, Rauch A, Arold ST, Woods CG, Komatsu M, Alkuraya FS. Brain. 2018 Jul 1;141(7):1934-1945. doi: 10.1093/brain/awy135. PMID: 29868776.

A Mendelian Form of Neural Tube Defect Caused by a De Novo Null Variant in SMARCC1 in an Identical Twin

Neural Tube Defects (NTDs) are common birth defects, second only to congenital heart defects, with a world-wide incidence of 1 in 1,000 live births. They are classical multifactorial disorders involving both environmental and genetic risk factors, although the precise nature of these factors and their interaction remains poorly understood. In this communication, a novel Mendelian form of NTD that corroborates previously published mouse models and highlights the importance of chromatin remodeling in neural tube closure was described.

The main finding of this project includes:

- A report of monozygotic twin with severe NTDs (occipital encephalocele and myelomeningocele) and a shared de novo, likely truncating, variant in SMARCC1.
- RTPCR analysis suggests the potential null nature of the variant attributed to nonsense-mediated decay.
- SMARCC1 is extremely constrained in humans and encodes a highly conserved core chromatin remodeler, BAF155.
- Mice that are heterozygous for a null allele or homozygous for a hypomorphic allele develop severe NTDs in the form of exencephaly.
- This is the first report of SMARCC1 mutation in humans, and it shows a critical and conserved requirement for intact BAF chromatin remodeling complex in neurulation.

Conclusion & Future Directions:

In conclusion, despite that the mechanism of SMARCC1-related NTD remains unclear, it likely involves impaired chromatin remodeling with resulting perturbation of gene regulation during critical stages of neurulation, as demonstrated in the previously reported mouse models. It is rather remarkable that despite being a core component of the chromatin remodeling complex in all tissues, the neural tube structures appear to be the most vulnerable to BAF155 deficiency, both in mouse and humans. This suggests a specific requirement for chromatin-remodelingmediated dynamic gene regulation during neurulation. Future studies will help delineate the nature of this epigenetic mechanism and the full phenotypic spectrum of SMARCC1mutations in humans.

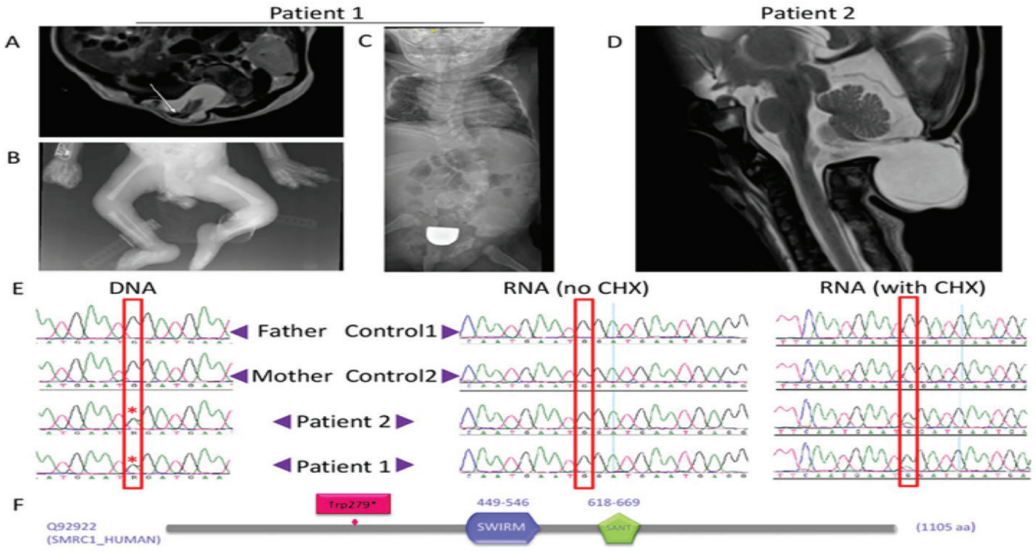


Figure: NTD phenotype observed in a monozygotic twin with a de novo, likely null, allele in SMARC1A. (A) T2-WI image of the index. **(B)** Right talipes calcaneovalgus deformity and left club foot seen in the index. **(C)** Left convex congenital lumber scoliosis secondary to abnormal segmentation. **(D)** T2-WI image of the twin sister. **(E)** Sequence tracing of PCR (left, DNA) and RTPCR without (middle) and with cycloheximide treatment (right) across the variant site.**(F)** Cartoon of SMARCC1 with the site of likely truncation indicated.

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

A mendelian form of neural tube defect caused by a de novo null variant in SMARCC1 in an identical twin. Al Mutairi F, Alzahrani F, Ababneh F, Kashgari AA, Alkuraya FS. Ann Neurol. 2018 Feb;83(2):433-436. doi: 10.1002/ana.25152. PMID: 29360170

Genomic and phenotypic delineation of Congenital Microcephaly

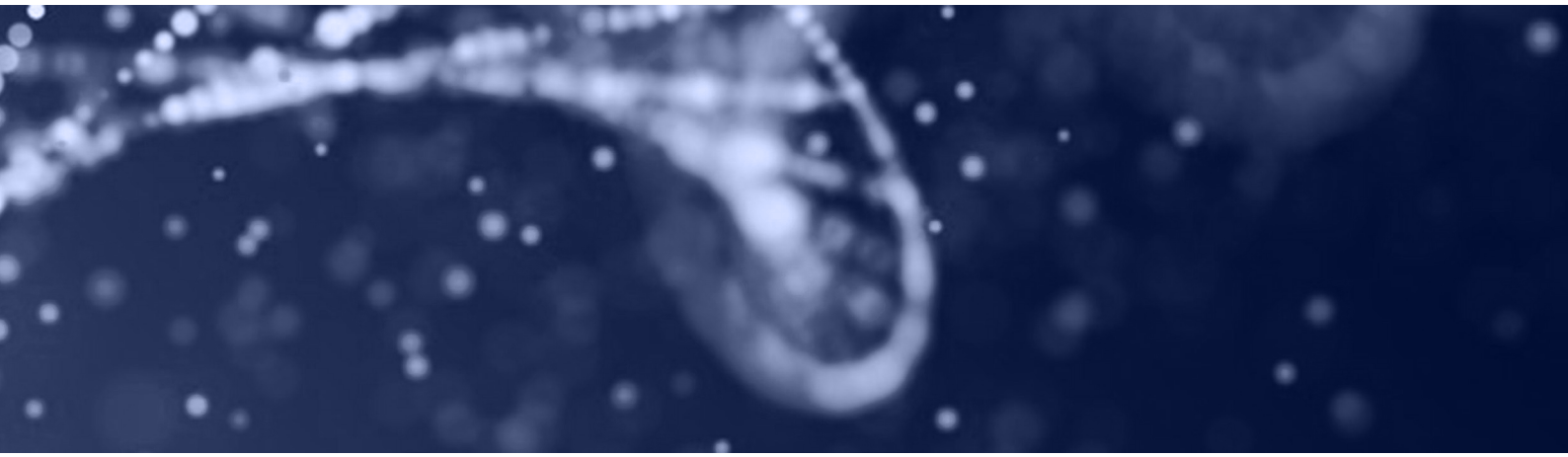
Congenital Microcephaly (CM) is an important birth defect with long term neurological sequelae. To the best of knowledge, there has not been any systematic phenotypic analysis of molecularly confirmed CM phenotypes to draw patterns that inform the clinical classification of genes that are critical for neurogenesis. This study made use of the large referral base of this current program in order to perform detailed phenotypic and genomic analysis of patients with Mendelian forms of CM.

The main finding of this project includes:

- Description of 150 patients (104 families) with 56 Mendelian forms of CM.
- Data showed little overlap with the genetic causes of postnatal microcephaly.
- Study showed that the broad definition of primary microcephaly —as an autosomal recessive form of nonsyndromic CM with severe postnatal deceleration of occipitofrontal circumference—is highly sensitive but has a limited specificity.
- Expanding the overlap between primary microcephaly and microcephalic primordial dwarfism both clinically (short stature in >52% of patients with primary microcephaly) and molecularly (e.g., we report the first instance of CEP135-related microcephalic primordial dwarfism).
- Expanding the allelic and locus heterogeneity of CM by reporting 37 novel likely disease-causing variants in 27 disease genes, confirming the candidacy of ANKLE2, YARS, FRMD4A, and THG1L, and proposing the candidacy of BPTF, MAP1B, CCNH, and PPFIBP1.

Conclusion & Future Directions:

This study presents a large cohort of molecularly characterized cases of congenital microcephaly and refines the phenotype of CM, expands its genetics heterogeneity, and informs the workup of children born with this developmental brain defect.



Variants in genes with established disease phenotypes in humans

RNU4ATAC, PCNT, AARS, BRCA2, PLK4, XRCC4, DDX11, RTTN, ASNS, NDE1, PQBP1, TSEN15, DONSON, PHGDH, PSAT1, TUBA1A, OCLN, PNKP, KATNB1, EP300, IGF1, CRIPT, SLC25A19, CTSD, BLM, VRK1, INO80, ERCC4, FOXG1, NSUN2, SBF1, RARS, ALDH6A1

59.6%

Variants in MCPH genes:

MCPH1, WDR62, CDK5RAP2, ASPM, STIL, CEP135, CEP152, CENPJ, CIT, MFSD2A

12.5%

Variants in genes with reported previously as candidate genes:

DNA2, CTU2, SPDL1, WDR4, PHC1, ANKLE2, THG1L, YARS, FRMD4A

12.5%

Variants in novel candidate genes:

BPTF, MAP1B, CCNH, PPFIBP1

3.8%

A chart showing the grouping and distribution of the variants identified in this cohort into four categories:

variants in MCPH genes, variants in genes with established disease phenotypes in humans, variants in genes reported previously as candidate genes, and variants in genes with no established disease phenotypes in humans.

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

Genomic and phenotypic delineation of congenital microcephaly. Shaheen R, Maddirevula S, Ewida N, Alsahli S, Abdel-Salam GMH, Zaki MS, Tala SA, Alhashem A, Softah A, Al-Owain M, Alazami AM, Abadel B, Patel N, Al-Sheddi T, Alomar R, Alobeid E, Ibrahim N, Hashem M, Abdulwahab F, Hamad M, Tabarki B, Alwadei AH, Alhazzani F, Bashiri FA, Kentab A, Şahintürk S, Sherr E, Fregeau B, Sogati S, Alshahwan SAM, Alkhalifi S, Alhumaidi Z, Temtamy S, Aglan M, Otaify G, Girisha KM, Tulbah M, Seidahmed MZ, Salih MA, Abouelhoda M, Momin AA, Saffar MA, Partlow JN, Arold ST, Faqeih E, Walsh C, Alkuraya FS. Genet Med. 2018 Sep 14. doi: 10.1038/s41436-018-0140-3. PMID:30214071

Expanding the Phenome and Variome of Skeletal Dysplasia

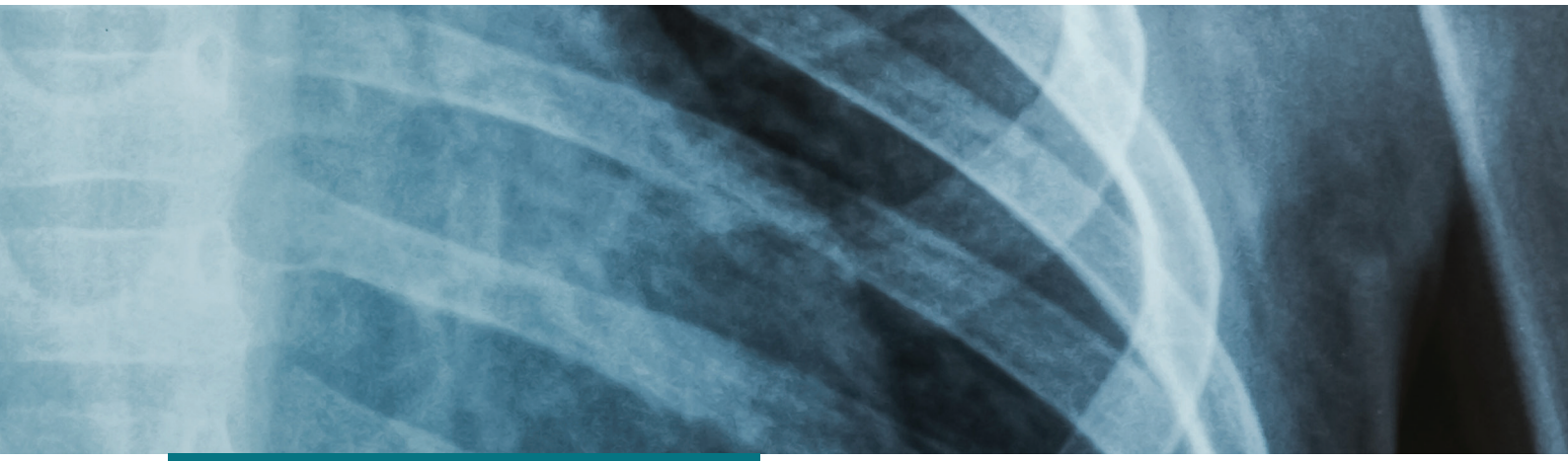
Heritable generalized disorders of bone and cartilage development, collectively known as skeletal dysplasias, are relatively common birth defects with an incidence of 1.3–3.2 per 10,000. Until recently, the diagnosis of skeletal dysplasia relied almost exclusively on careful phenotyping, often aided by consultation with experienced radiologists. However, the advent of genomic tests has the potential to ease this bottleneck because these tests scan a large number of target disease genes irrespective of the suspected clinical diagnosis. This study provides detailed phenotypic and genotypic features of large cohort of molecularly characterized individuals with skeletal dysplasia.

The main finding of this project includes:

- The analysis revealed 224 pathogenic/likely pathogenic variants (54 (24%) of which are novel) in 123 genes with established or tentative links to skeletal dysplasia.
- Five genes were proposed as candidate disease genes with suggestive biological links (WNT3A, SUCO, RIN1, DIP2C, and PAN2).
- Phenotypically, this cohort spans 36 established phenotypic categories by the International Skeletal Dysplasia Nosology, as well as 18 novel skeletal dysplasia phenotypes that could not be classified under these categories, e.g., the novel C3orf17-related skeletal dysplasia.
- Description of novel phenotypic aspects of well-known disease genes, e.g., PGAP3-related Toriello–Carey syndrome–like phenotype.
- A strong founder effect for many genes in this cohort was noted, which allowed to calculate a minimum disease burden for the autosomal recessive forms of skeletal dysplasia in our population (7.16E-04), which is much higher than the global average.

Conclusion & Future Directions:

In conclusion, through sharing the phenotypic and genotypic data of a large molecularly characterized skeletal dysplasia cohort, this study will contribute in improving the diagnostic rate of patients with these conditions.



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

Expanding the phenome and variome of skeletal dysplasia.

Maddirevula S, Alsahli S, Alhabeeb L, Patel N1, Alzahrani F, Shamseldin HE, Anazi S, Ewida N, Alsaif HS, Mohamed JY, Alazami AM, Ibrahim N, Abdulwahab F1, Hashem M, Abouelhoda M, Monies D, Al Tassan N, Alshammari M, Alsagheir A, Seidahmed MZ, Sogati S, Aglan MS, Hamad MH, Salih MA, Hamed AA, Alhashmi N, Nabil A, Alfadli F, Abdel-Salam GMH, Alkuraya H, Peitee WO, Keng WT, Qasem A, Mushiba AM, Zaki MS, Fassad MR, Alfadhel M, Alexander S, Sabr Y, Temtamy S, Ekbote AV, Ismail S, Hosny GA, Otaify GA, Amr K, Al Tala S, Khan AO, Rizk T, Alaqeel A, Alsiddiky A, Singh A, Kapoor S, Alhashem A, Faqeih E, Shaheen R, Alkuraya FS. Genet Med. 2018 Apr 5. doi: 10.1038/gim.2018.50. PMID: 29620724

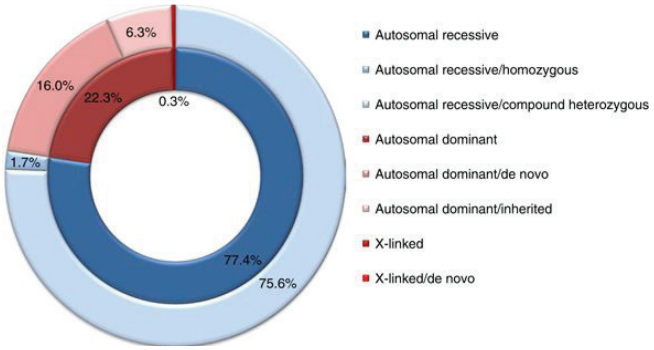


Figure: Doughnut chart showing the proportion of autosomal recessive (homozygous and compound heterozygous shown separately), dominant, and X-linked (inherited and de novo shown separately) conditions in the study cohort.

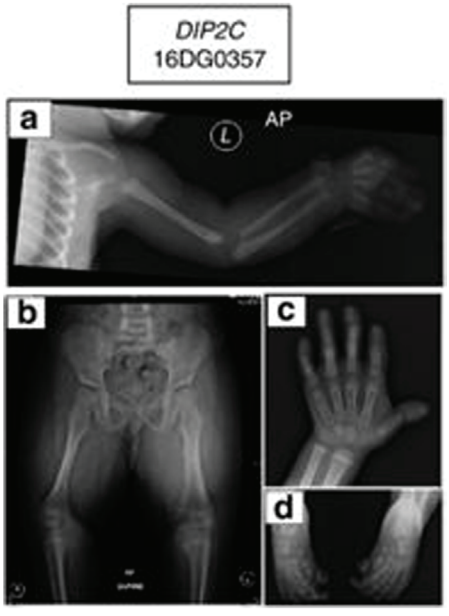


Figure (A–B): A patient with a mutation in DIP2C, **(C)** clinodactyly with shortening of metacarpal bones, **(D)** bilateral metatarsus adduction, bilateral shortening of 1st metatarsals

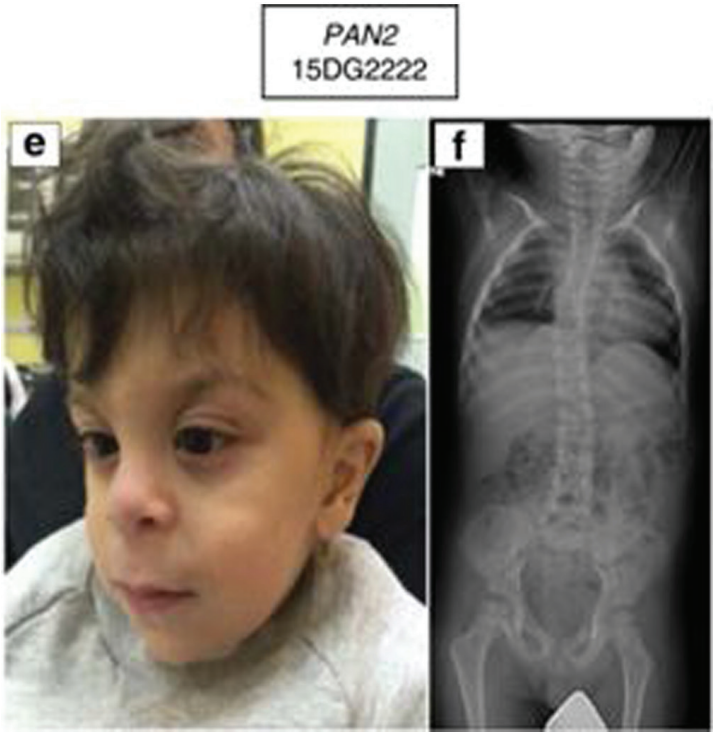


Figure (E and F) A patient with a mutation in PAN2showing plagiocephaly

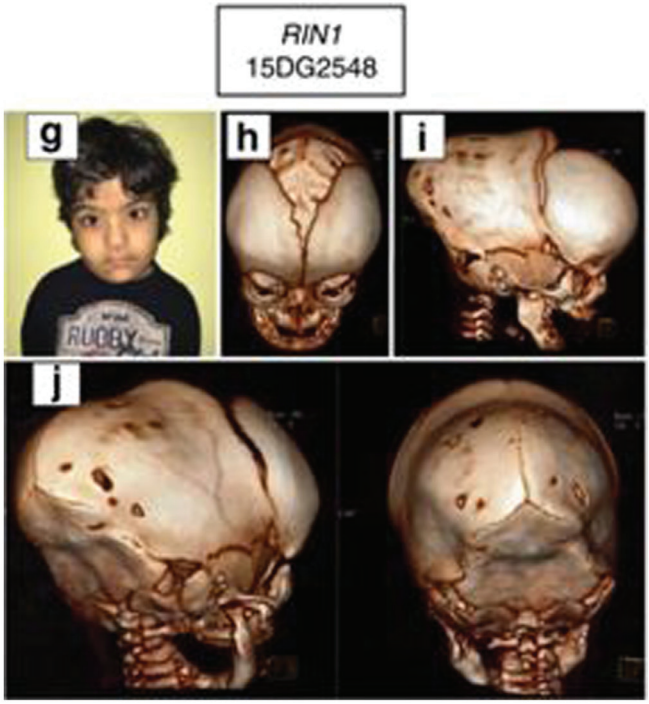


Figure (G and J) A patient with a mutation in RIN1 showing plagiocephaly

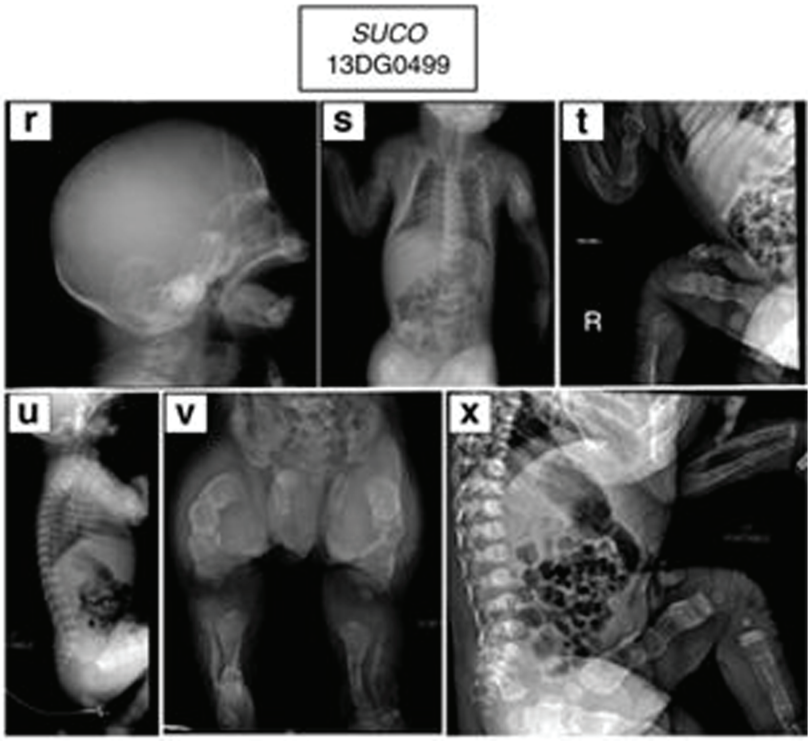


Figure (K–Q) A patient with a mutation in WNT3A

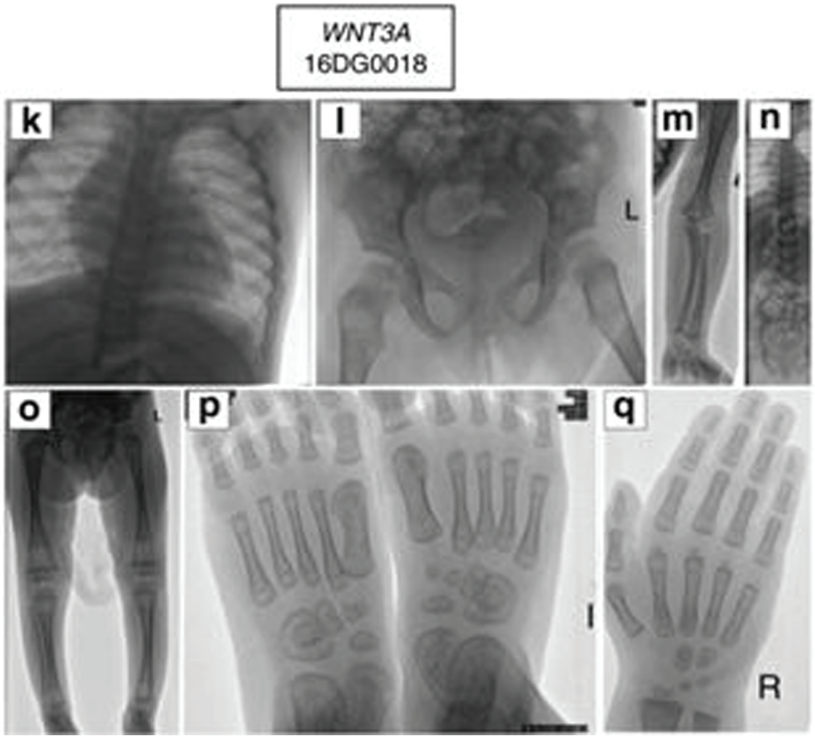


Figure (R–X) A patient with a mutation in SUCO



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

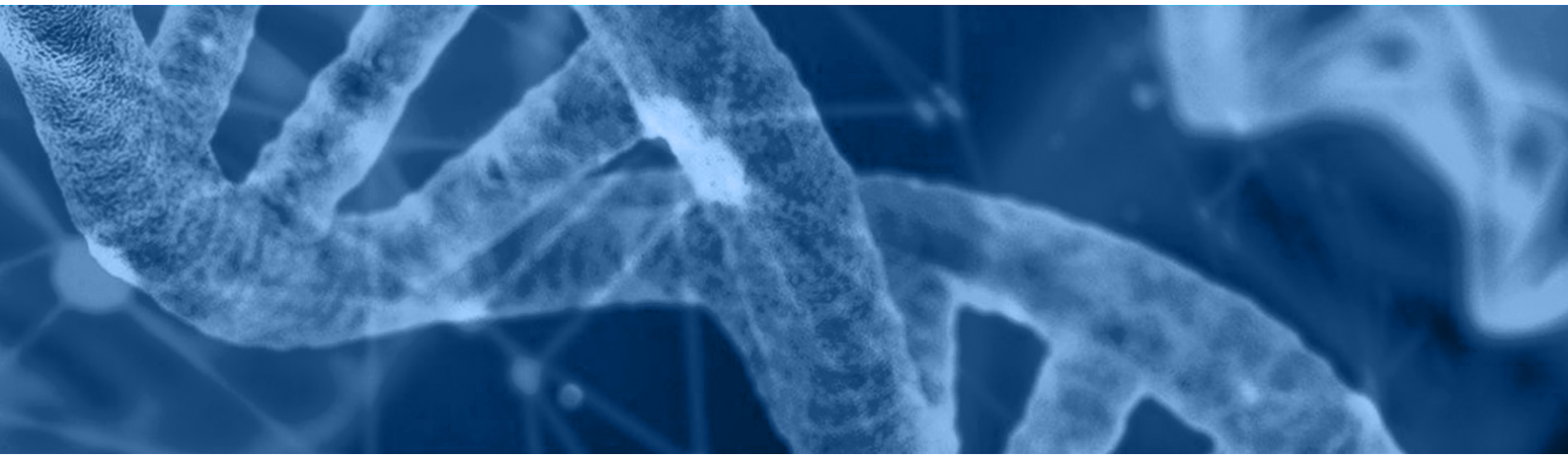
The genetic factors contribute with 70% of the loss of vision and low vision cases in Saudi children. Majority of vision loss in Saudi Arabia is likely to follow a monogenic, specifically autosomal recessive form of inheritance. This is attributed to high rates of inbreeding and consanguinity. Given 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.

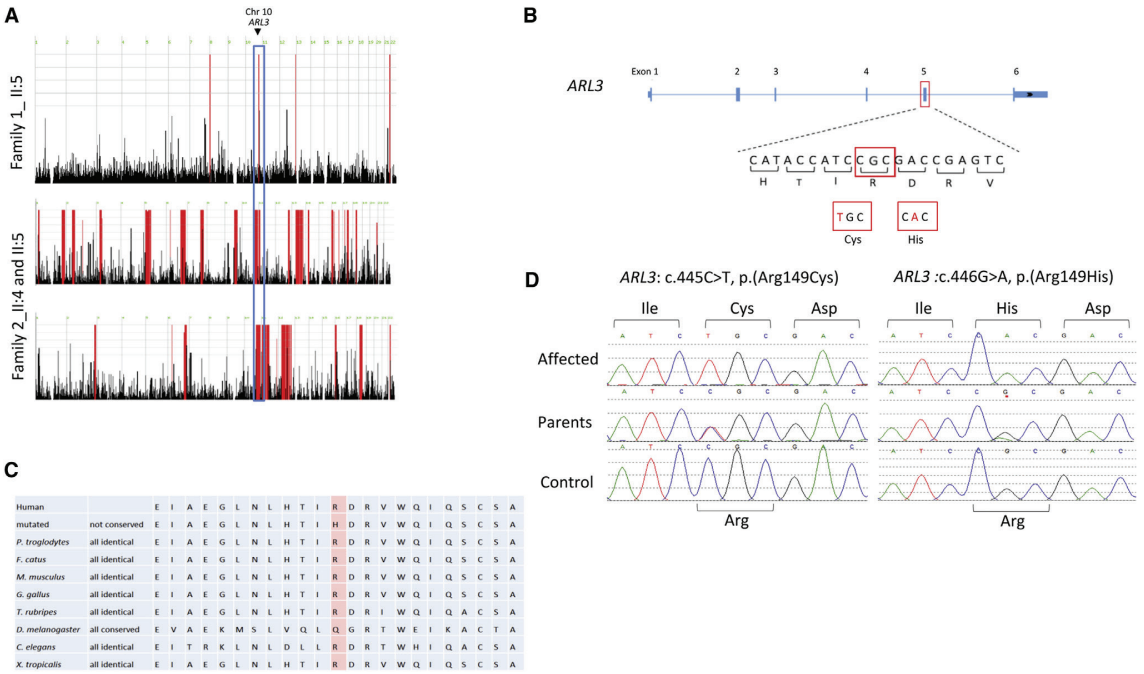


Figure: Molecular Genetic Investigations of the Two JBTS-Affected Families.

(**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.

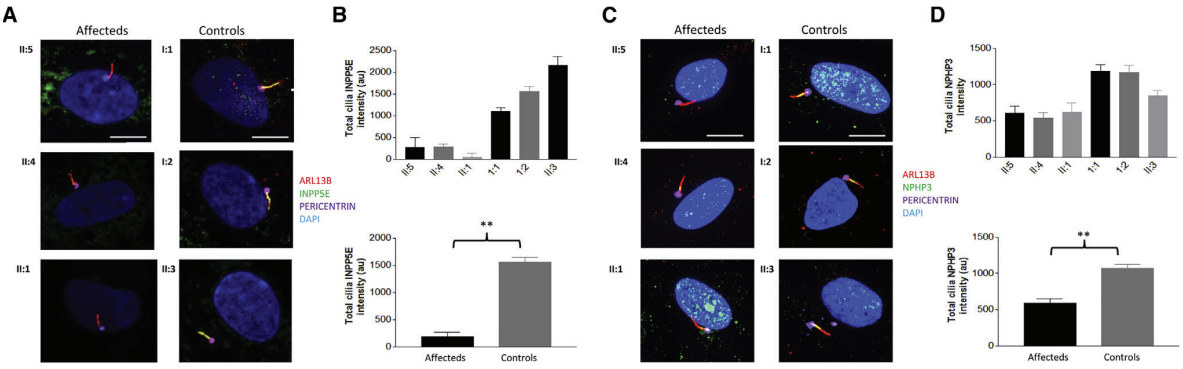


Figure: Characterization of Ciliary Phenotype in ARL3-Mutant Fibroblasts from Family 2.
(A and C) Affected and control fibroblasts were observed under high-power immunofluorescence for determining ciliary expression of (A) INPP5E and (C) NPHP3. **(B)** Quantification of ciliary localization of INPP5E (**$p < 0.0001$, 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).

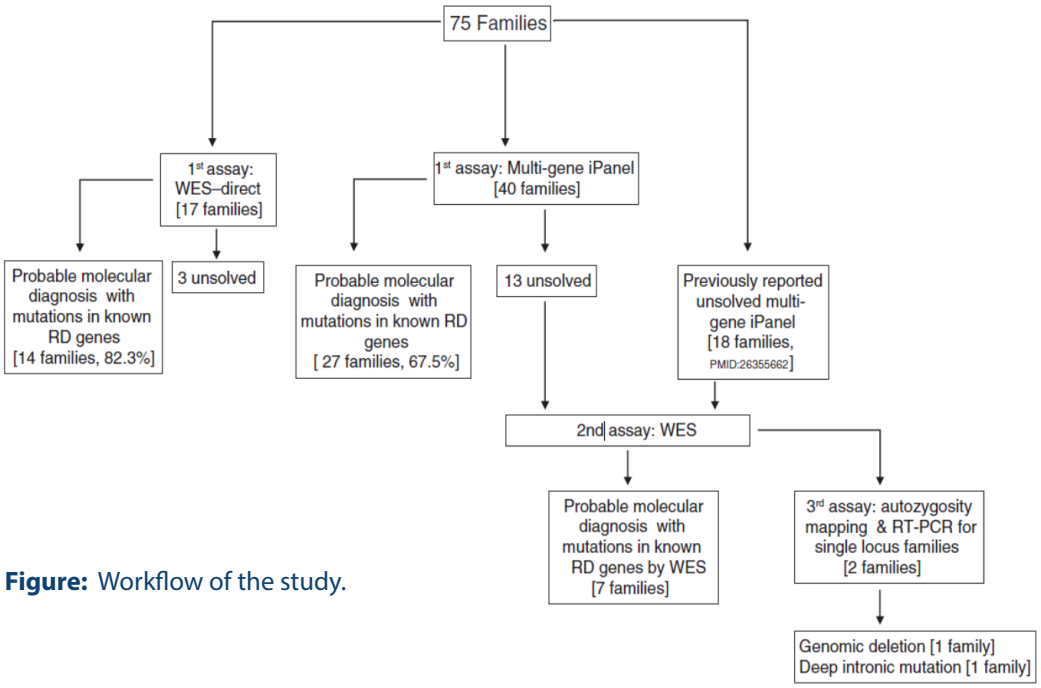


Figure: Workflow of the study.

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.

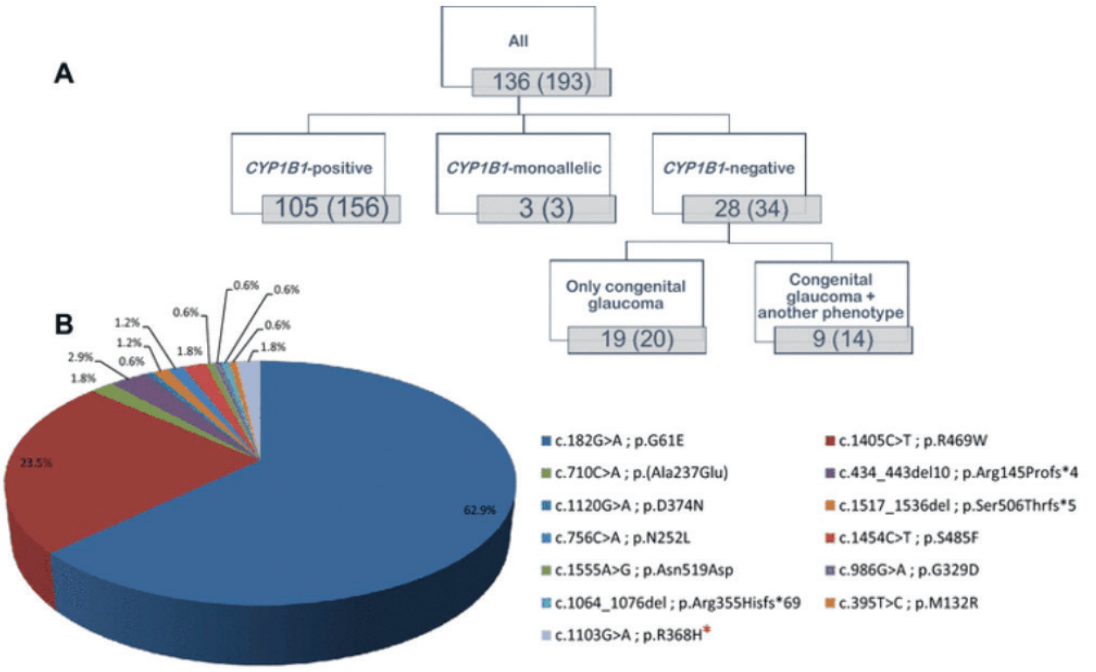


Figure: **(A)** Distribution of CYP1B1 mutations in the study cohort. Numbers denote families and numbers in parenthesis denote absolute counts of individuals. **(B)** Pie chart distribution of 13 mutations identified in CYP1B1

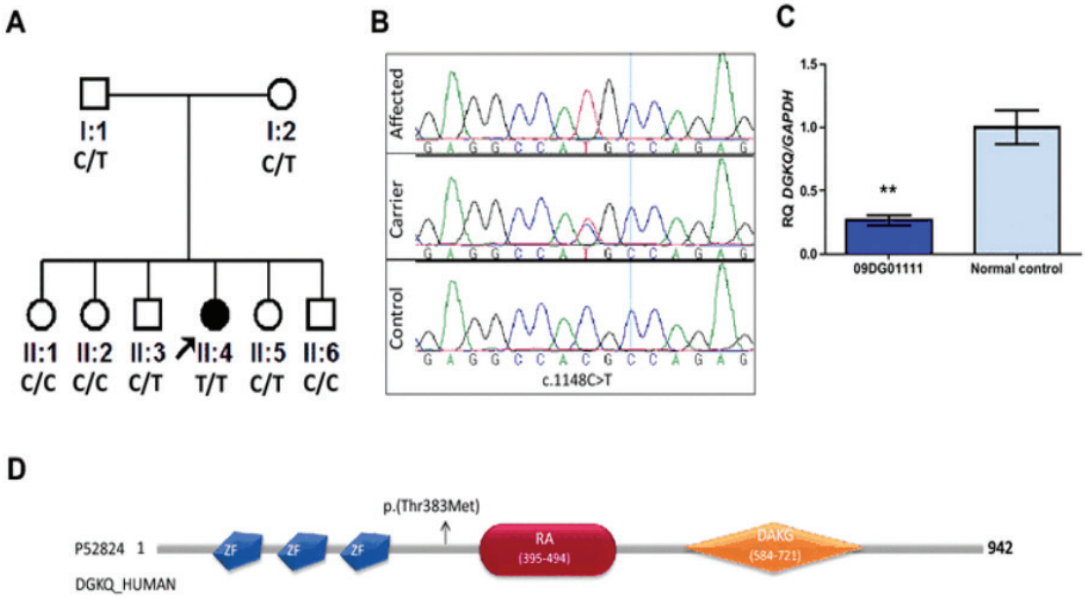


Figure: **(A)** Pedigree of the family with congenital glaucoma and a novel DGKQ variant. **(B)** Sequence chromatogram of the novel DGKQ variant. **(C)** qRT-PCR for DGKQ expression in LCL in patient 09DG01111 with a missense mutation in this candidate gene compared to three normal control reveals >70%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

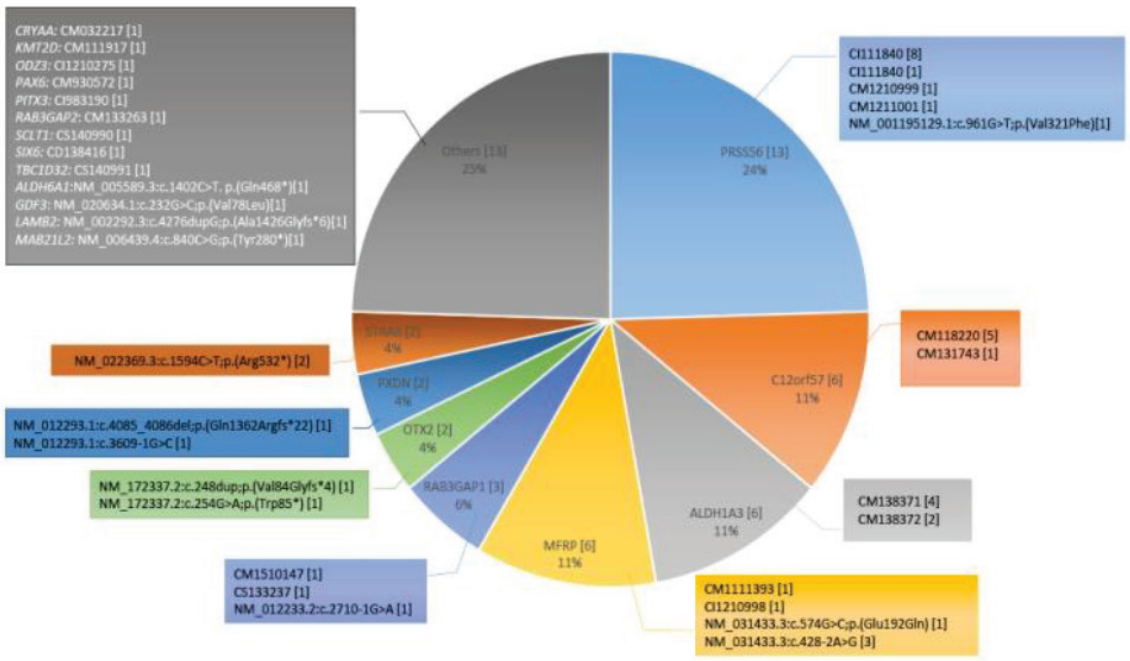


Figure: Pie chart illustrating the distribution of mutations across 21 disease causing genes known to cause microphthalmia. Numbers in square brackets indicate the occurrence of that particular mutation within the cohort. HGMD accession numbers are noted for previously reported mutations, while full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

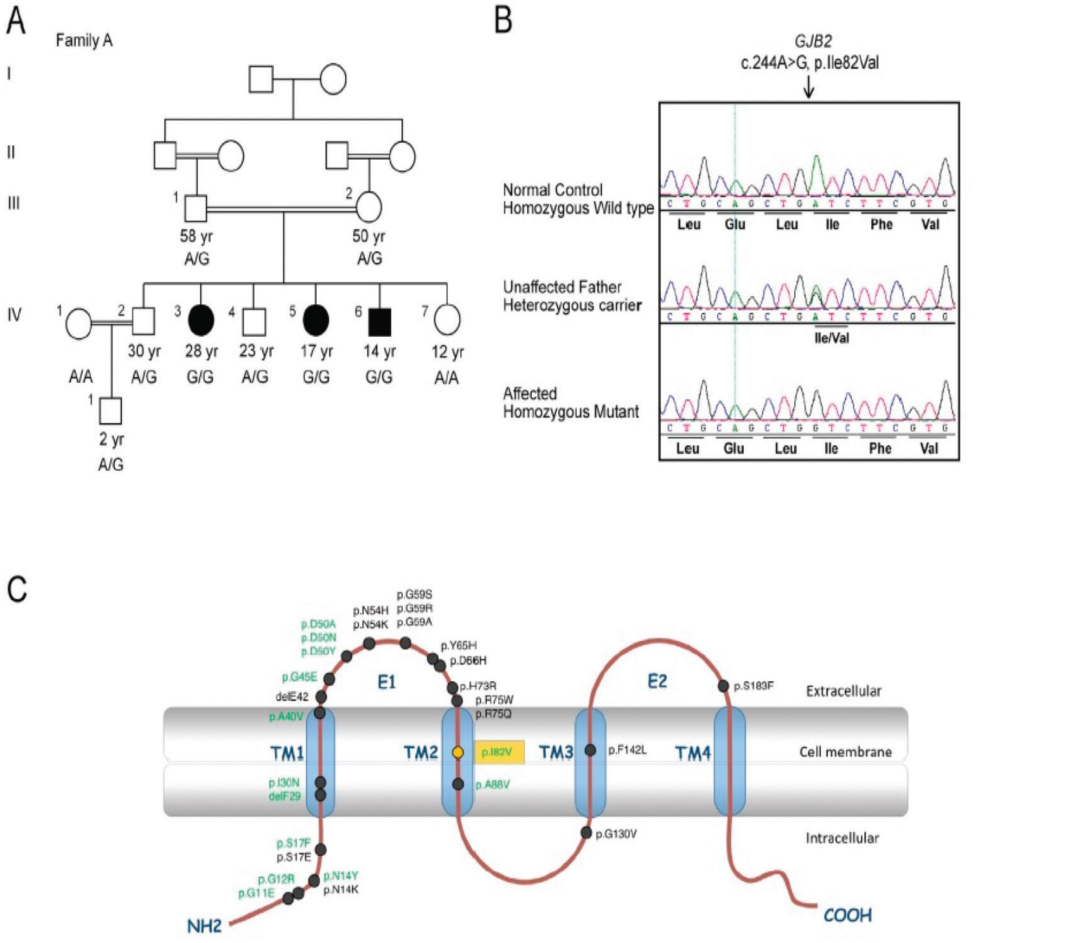


Figure: (A) Pedigree and the genotypes of family members with autosomal recessive KID syndrome. (B) GJB2 Sequence chromatograms of normal control. (C) Connexin 26 mutations causative for several syndromic forms of hearing loss associated to skin problems.

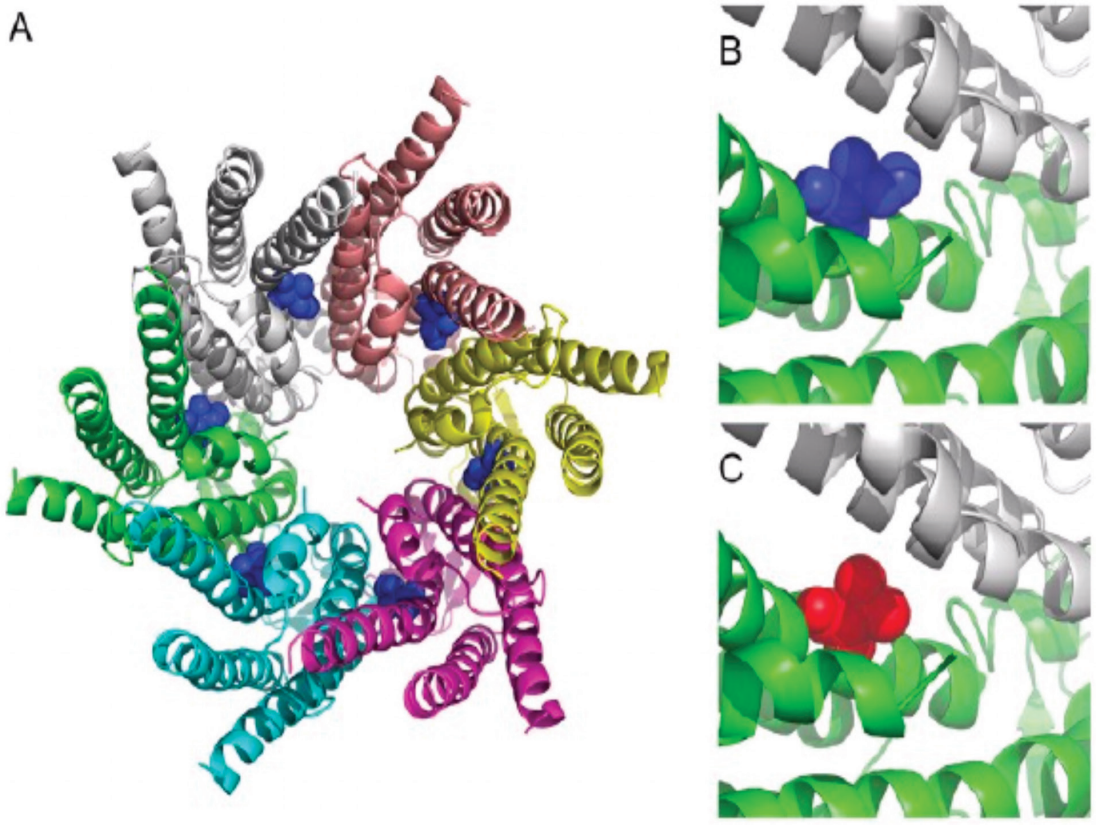


Figure: (A) The Connexin (6 subunits) and the oligomerization pattern of Cx26 hexameric chains are depicted. (B and C) show the structures of the wild-type residue.

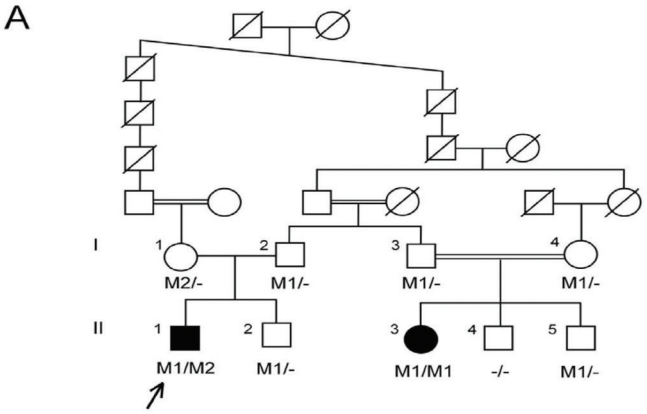


Figure: (A) Pedigree of the family showing the segregation of MYO7A mutations with Usher syndrome.

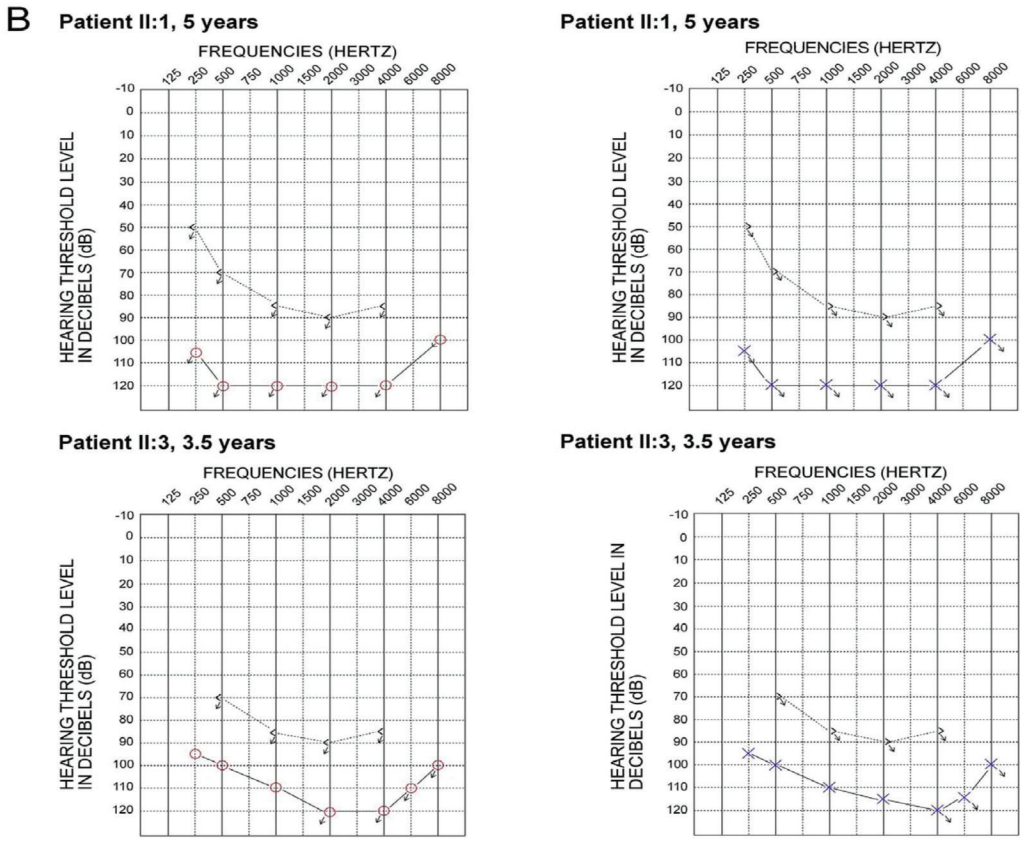


Figure: (B) Representative pure-tone air and bone conduction audiometric results of Patients II:1 and II:3.

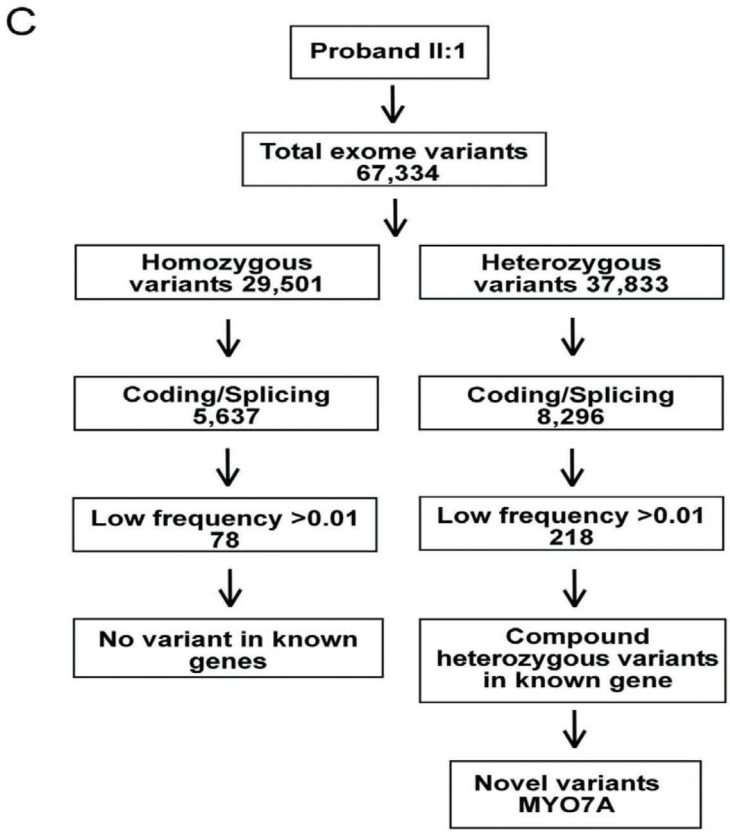


Figure: (C) Novel variants in MYO7A were detected as the only possibly causative variants.

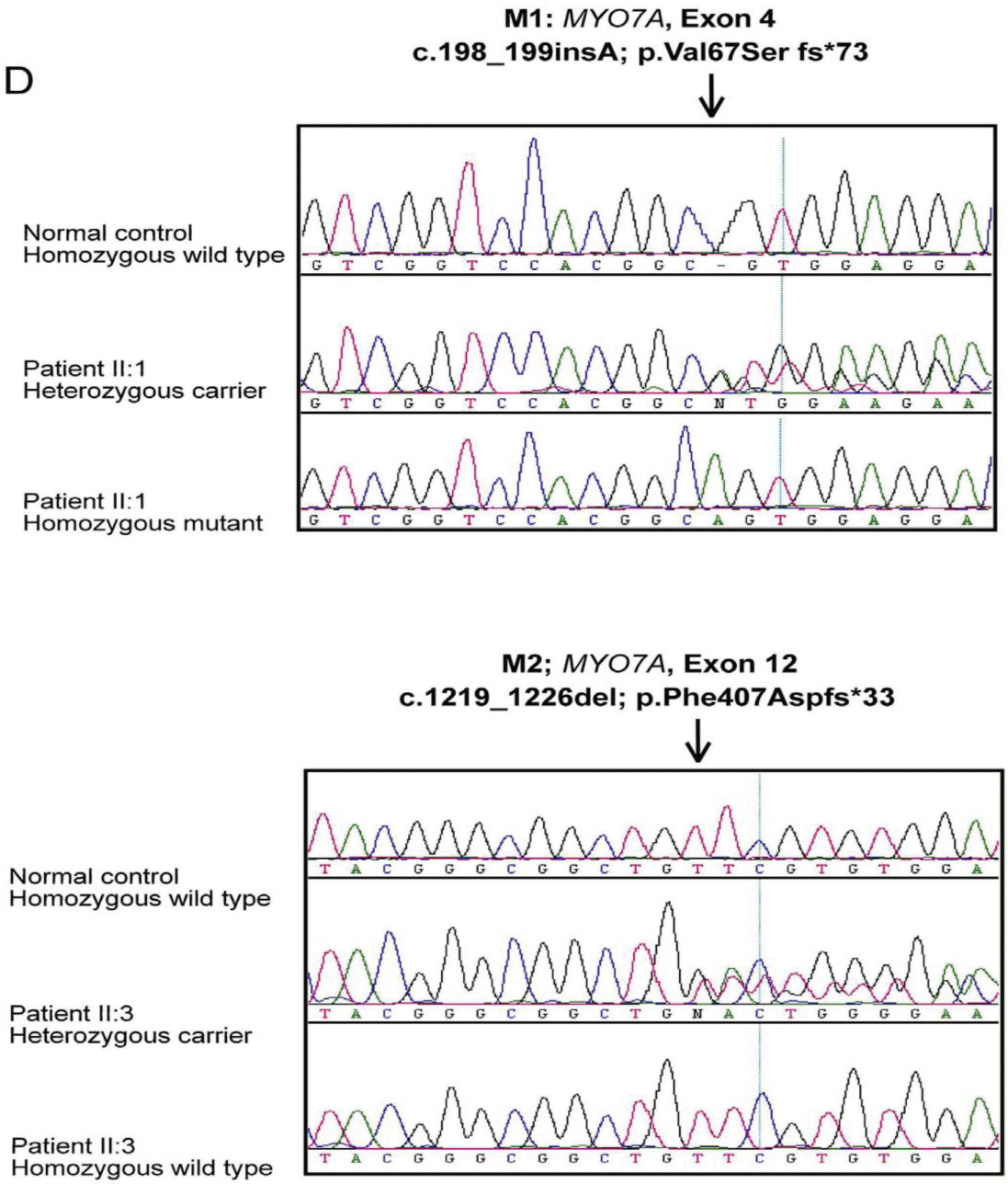


Figure: (D) Electropherograms showing the Sanger sequencing confirmation of the mutations identified in the proband by CES. **(E)** A full-length wild type myosin-VII A protein structure.

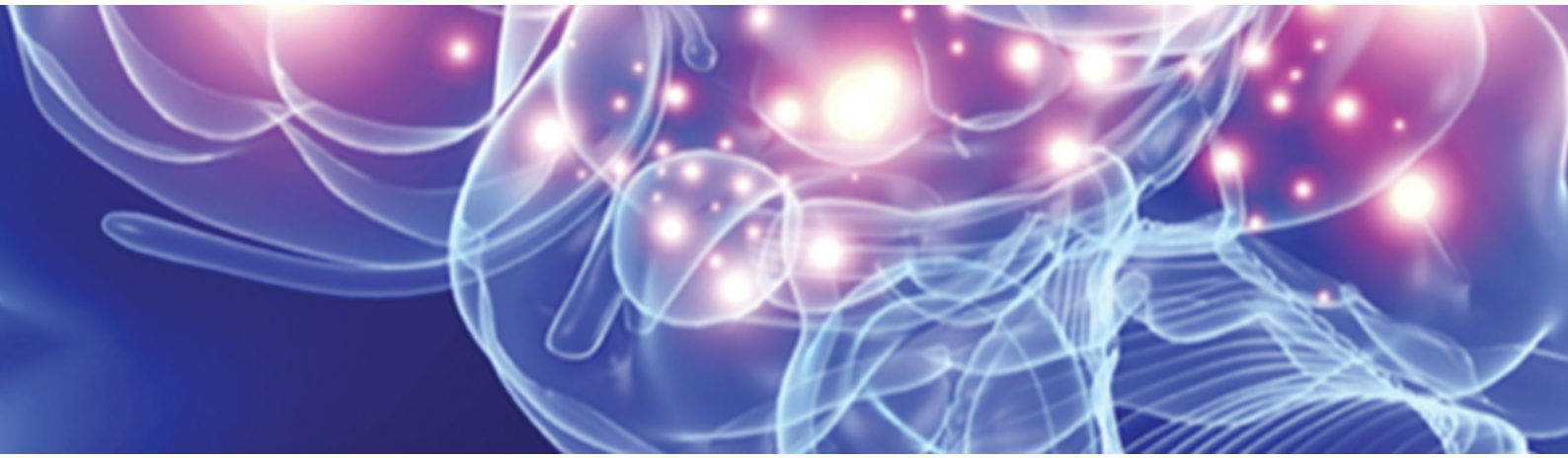


Programs

Psychological Health

In 2018, the project team worked with Harvard University and University of Michigan, Ann Arbor on finalizing the survey sample weighting details. Weighting adjustment is a correction technique used in statistical analysis to assign adjustment weights to survey respondents. Using this technique, respondents who were under-represented or over-represented in the sample were 'weighted' to represent the actual Saudi population. This technique makes the findings of our study stronger and more precise as it better represents every Saudi in the country. Following this, statistical analyses were conducted and began reviewing the results. Using these findings, the investigators are working on the core publications that will inform the health community, the policy makers, and the public, about the status of mental health in KSA.

At the same time, the investigators are working on publications related to the survey methodology accomplishments of the SNMHS, which are one of the first of their kind in the Gulf region. Survey methodology and techniques are still scarcely researched in the Gulf. This project is one of the pioneers in the Gulf to share its high-quality survey methodology experience with the scientific community. To-date, the investigators have published three articles on this topic in high ranking peer-reviewed scientific journals.



Achievements During 2018 :

1. External Reviewers (KACST):

The project reports received high praise from reviewers at King AbdulAziz for City for Science and Technology (KACST) for two of interim progress reports. For the 2017 review, a score of 26/30 with an excellent rating was awarded with reviewer's comment: 'project progress and report documentation exceed expectations. For the 2018 review, two reviewers gave a score of 29/30 and 26/30 respectively, both excellent ratings where one of the reviewer's noted that 'this project will have a significant impact on the knowledge and implications for services related to mental health in Saudi Arabia'.

2. Data Analysis:

Data analysis is currently being carried out by the World Mental Health Data Analysis Center at Harvard School of Medicine. Their team of specialized advanced survey analysts, epidemiologists and statisticians are working with the PI to ensure all aims of the project are addressed and accomplished, by implementing a detailed data analysis plan and roadmap, based on the needs and objectives. For some results, additional verification was decided upon, which is accomplished by conducting additional interviews with Saudi respondents using a gold standard interview known as SCID (Structured Clinical Interview for DSM-5).

3. 3) Research Collaboration with the University of Michigan Ann Arbor:

Project team has made great progress in 2018 while working closely with University of Michigan, Ann Arbor on the following aspects:

a. Data management, carrying out data cleaning and weighting on the collected survey data so as to perform statistical analyses.

b. Survey methodology papers for scientific journal publication.

c. Coding CIDI instrument open-ended questions. The coding will be used to analyze results for a potential paper using the SNMHS data on the topic of satisfying, a new area of survey research which explores respondent thought processes during an interview.

4. Genetics and Scientific Advancement:

The SNMHS is one of the distinctively scientific studies participating in the World Mental Health Survey Consortium, which has collected over 2000 saliva samples from its respondents after obtaining an additional consent from them.

All saliva samples collected during the interviews from all areas of KSA were sent to KFSH&RC for extraction and freezing until further analyses. The DNA specimens extracted from these samples will be used to study genetic risk factors for mental health conditions prevalent in the Saudi population.

5. Principal Investigator of SNMHS became Visiting Faculty at Harvard University School of Medicine:

As a result of several years working closely with Professor Ron Kessler and his team at Harvard School of Medicine, in July 2018, Dr. Yasmin Altwaijri became a Visiting Faculty at Harvard University – School of Medicine, Boston USA. During 2018 she was working closely with the data analysis team (data analysts, epidemiologists, and biostatisticians) at Harvard School of Medicine, developing each facet of the analysis plan, reviewing them with the team, and discussing the output and results. She is also in the process of forming potential collaborations with experts in the field for publications using the results of the SNMHS.

6. Conferences and Workshops:

- The WHO World Mental Health Initiative Annual Meeting held at Harvard University, July, 2018, Boston, USA.
- The 5th International Conference on Disability and Rehabilitation, organized by King Salman Center for Disability Research, April 1-2, 2018, Riyadh, KSA.
- The 2018 MENA Summit, February 7-8, 2018, Abu Dhabi, UAE.
- The 2nd Middle East Psychological Association Conference and Expo held on April 12th-14th, 2018 in Dubai, UAE.
- The Ethereal Summit NY which was held from 11 - 12 May 2018 at the Knockdown Center, Maspeth, New York, USA.

7. The Training Workshops:

- September 2, 2018: 1st SCID Training Workshop
- September 2018: Clinical Psychology interns at Prince Nora University were introduced to the SCID interview; trainees begin conducting the phone interviews with the survey participants (sub-sample of the original sample).
- October 2018: 2nd SCID Training Workshop (refresher) training. The interviewers then conducted phone OCD-SCID interviews for

and additional batch of survey participants.

- November 2018: with the involvement of the Harvard University team, a workshop was conducted to discuss the notes and diagnoses of SCID interview results. These results are compared to the Yale-Brown Obsessive-Compulsive Scale, which is part of the Saudi survey CIDI instrument. Comparison results will be used to fine tune the OCD prevalence results, and its margin of errors in the population.

- December 2018: Training Workshop: SCID- Separation Anxiety Disorder (SAD). Following the training the interviewers started the SAD-SCID interviews for a sample of 75 cases.

8. Publications:

In an effort to highlight the efforts exerted by the Kingdom of Saudi Arabia to care for the mental health and the efforts exerted by KSCDR on this important national project, the investigators are in discussion with a high ranking journal in psychiatry, to publish a "special issue about the Saudi National Mental Health Survey". It will include several scientific manuscripts, which have resulted from the project. A peer-reviewed manuscript was published in 2018:

Mneimneh, Z. N., Hibben, K. C., Bilal, L., Hyder, S., Shahab, M., Binmuammar, A., & Altwaijri, Y. (2018). Probing for sensitivity in translated survey questions: Differences in respondent feedback across cognitive probe types. Translation & Interpreting, 10(2), 73-88. https://doi.org/10.12807/ti.110202.2018.a06

Future Directions:

- Continue collaboration with Harvard University School of Medicine, World Mental Health Data Analysis Center, on the data analyses for the survey.

- Continue working on writing publications using the psychology results from the data analyses.

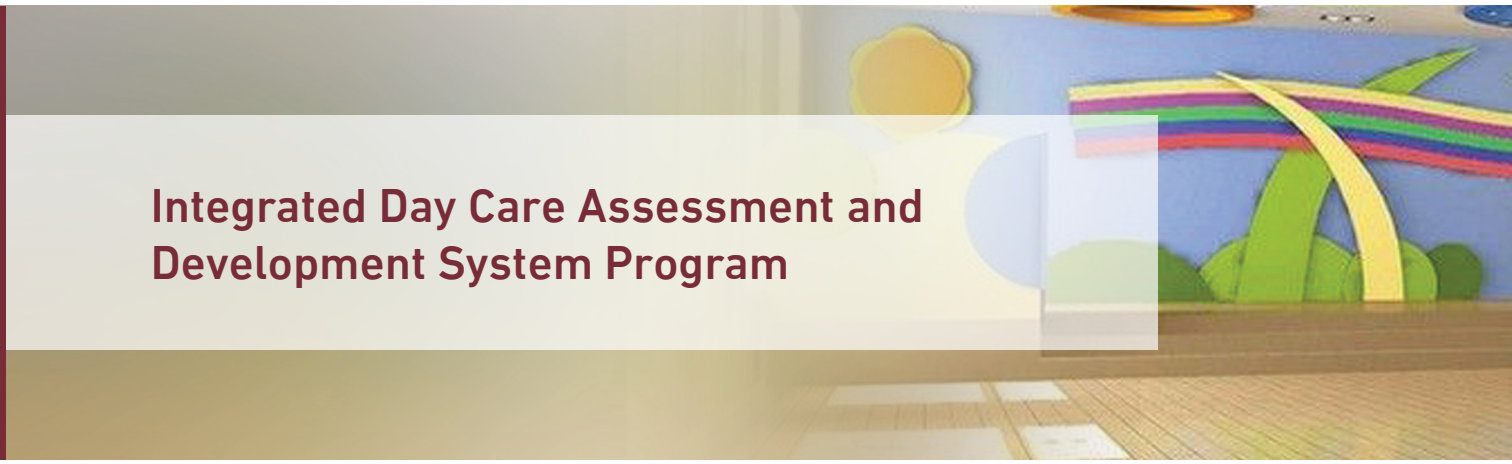
- Continue working on publications related to the survey methodology accomplishments and experience of the SNMHS.

- Begin working on exploratory in-depth analyses of data.

- Additional grant funding will be sought to support the continuation of data analysis.

- Additional funding will be sought, for the genetic analysis aspect of the survey.

- Discussing the possibility to incorporate additional analytical tools and instruments using advanced analytics (Artificial Intelligence and Machine Learning), which will allow to leverage the information for the project data, providing actionable insight to enable intelligent automation for mental health disease prevention, early detection and decision making.



Integrated Day Care Assessment and Development System Program

The daycare centers' assessment system is a comprehensive, integrated system, which assesses and improves the operations, programs, and services provided to children with disabilities and their families by providing the training and guidance needed to improve these processes, a critical factor in bringing about changes in the centers serving these groups of children. And to enhance the performance of centers This document created a kind of motivation for these centers, where all centers desired to receive training according to the criteria and terms of this program so that they would always be within the typical range.

The system was developed for the Ministry of Labor and Social Development in Saudi Arabia by a team composed of officials affiliated to the King Salman Center for Disability Research in Riyadh and others affiliated with the Academy of Scientific Development, as well as various contributions from many stakeholders. The system involves both the Ministry of Labor and Social Development and the daycare center (s) in the evaluation and improvement process to support the operations, programs, and services provided to disabled children and their families through these centers. This document describes how this system was developed.

Current status:

- The Ministry of Labor and Social Development seeks to establish clear rules and standards that follow the new regulations of the Ministry and a practical framework to ensure an objective and comprehensive evaluation of care centers throughout the Kingdom to achieve the vision of the Kingdom 2030.
- Complete the scientific research plan and work on developing the measurement criteria for the program.
- Accordingly, it was agreed to rely on the evaluation criteria included in the guidelines for the evaluation system of daycare centers approved by the King Salman Center for Disability Research and to review and develop the standards in order to start evaluating daycare centers.
- And through these workshops and meetings with researchers and consultants from the King Salman Center for Disability Research and project consultants by the Ministry to take the views and discussions regarding evaluation criteria.
- Agreeing upon any amendments on standards made by the leading team

Academic Training Program:

A number of workshops and training courses were organized to:

- Discuss some of the criteria for the assessment tool for the current and future status (the Centers Evaluation Program after changing regulations).

- Aims at organizing daycare centers, encouraging the private sector to participate in the care and rehabilitation of persons with disabilities, and developing programs and services provided to them and follows the regulations and standards of evaluation programs.
- Presentation of workshops and lectures aimed at introducing the program
- Accurate and precise definition according to international standards, commensurate with the local community and services provided at this center.
- Continuous follow-up and supervision on the maintenance of information related to whole officials and stakeholders.

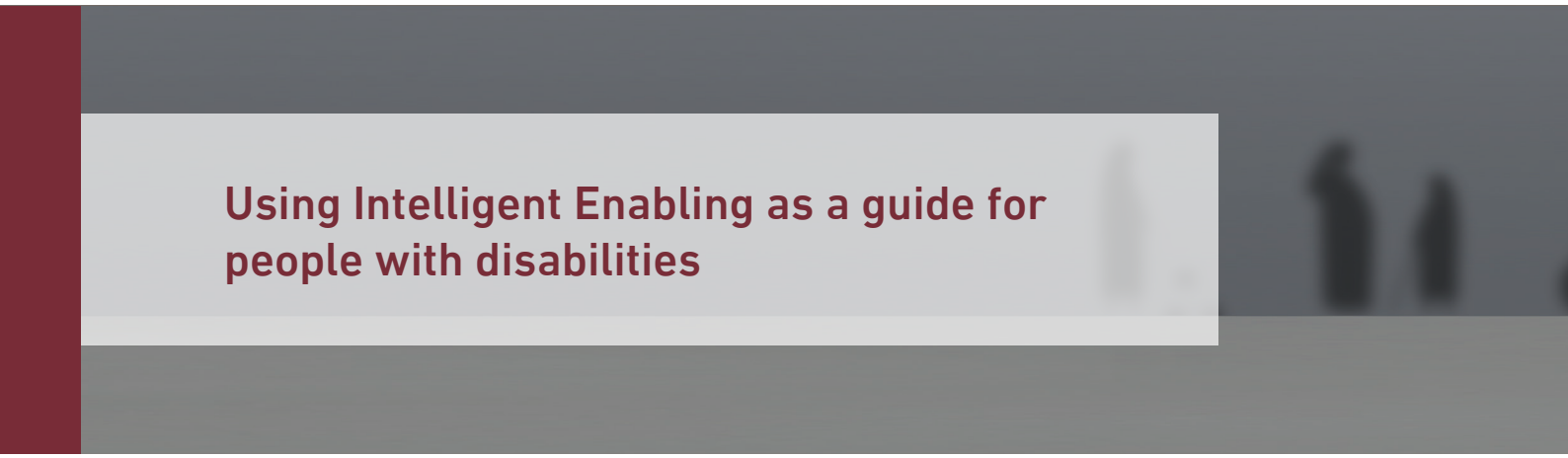
Courses and training workshops for the year 2018:

- Three general training courses for specialists and officials of the Ministry of Labor and Social Development

- eight workshops to Business and procedures Development Management Team of Ministry of Labor and Social Development
- Three training courses for center managers on the self-assessment process and improvement plan for administrators and teachers from daycare centers for people with special needs.

- 15 training courses for surveyors from the Ministry of Labor and Social Development supervisors on the evaluation program.

These activities were attended by (789 participants) specialists and officials from the Department of Labor Development from the Ministry of Labor and Social Development and from associations and centers, supervisors from the Ministry and managers of centers from different regions of the Kingdom of Saudi Arabia.



Using Intelligent Enabling as a guide for people with disabilities

Under the guidance of His Royal Highness Prince Sultan bin Salman bin Abdulaziz, Chairman of the Board of Trustees of the King Salman Center for Disability Research, to provide Intelligent applications as a platform to serve people with disabilities.

Project description:

In a new gesture used for the first time in the kingdom, coordinated with a competent company to use Intelligent Enabling Service, which allows persons with disabilities easy to move within any building by using mobile phones after providing a special code, and will provide them self-reliance and full independence Without seeking assistance and support in their movement between the halls, the venues of sessions and workshops, and the provision of services, as well as the provision of information and the identification and accessibility of places.

The techniques of Artificial Intelligence or Intelligent Enabling have created exceptional solutions in enabling people with disabilities and have opened up new horizons to empower them, and we look forward to enhancing the use of all the services that the center provides, and to create and implement enabling and supportive environments for persons with disabilities To the extent possible to enable them to overcome their challenges and their full involvement in society, which we consider to be an integral part of the Centre's objectives and the achievement of its strategy, in an intelligent format that facilitates the access of beneficiaries.

The Intelligent Enabling Service was launched at the Conference to serve persons with disabilities, where persons with disabilities were able to access this service as soon as they reached the service providers and provided them with their own code, and they rely on Bluetooth technology and form additional features to access information and find ways For all facilities, the deaf will be able to track alerts through vibration, and the features of wheelchair users enable them to access different sections and facilities by choosing wheelchair-accessible routes, The blind accessibility features enable them to navigate more freely by warning The way of sound from the obstructions around him.

Related Project:

Guidelines for comprehensive access standards for evacuation (fires and natural disasters)

A guide for the training of civil defense centers, related bodies, hospitals, disabled persons, their guardians, and workers in the centers for the care and rehabilitation of disabled persons to deal with incidents of fire and natural disasters and to carry out evictions with the latest special equipment and devices for the disabled and the elderly.

Newborn Screening Program 2018

المختبر الوطني للكشف المبكر على حديثي الولادة
National Laboratory for Newborn Screening

The Newborn Screening (NBS) is one of KSCDR supported Programs and considered to be one of the most effective public health programs that has an ultimate goal for prevention of mortality, morbidity, and disabilities through early detection of disorders that are potentially treatable and before the development of symptoms, thereby, allowing for early intervention and case management. Currently, the Saudi National Newborn Screening Program screens for 17 metabolic and endocrine disorders. Prevalence of these conditions in Saudi Arabia is estimated to be around one affected newborn per 1000 screened and considered to be one of the highest prevalence worldwide.

Screening is achieved through the analysis of few drops of blood collected from the newborn's heel and spotted on specific filter paper cards containing all required demographics of the infant and parents. The collection is mostly done after 24-48 hours of birth. Screening test includes certain metabolic and endocrinal disorders. If the initial and the retest of the first dried blood sample (DBS) turn to be positive, then a recall/ second DBS sample along with other samples (urine or plasma) if applicable are requested of the same newborn from the referral hospital. When received, if the analysis result is still positive an abnormal report will be generated and sent to hospitals. If further confirmation testing is needed, then a specific diagnostic test for the disorder will be initiated to confirm the diagnosis (figure1).

Achievements of this project includes

- The screening panel of the NBS Program includes 17 disorders (see table 1).
- One additional Hospital joined giving a rise of a total of more than 190 hospitals participated in the program.
- The total number of newborns screened during 2018 was 80069. The distribution of the samples throughout regions is shown in (figure 2).
- The total number of cases detected during 2018 was 47 cases. The distribution of detected cases per region is illustrated in (figure 3A & B).
- CH then CAH followed by MMA were the highest detected cases during 2018. (Figure 4) showed the number of cases detected during 2018.
- The total number of screened Newborns since the beginning of the Program was 1182468.
- The accumulative disorders prevalence per 100000 newborns screened from August 2005 until December 2018 of each disorder is demonstrated in (figure 5).
- Total number of received and tested sick babies during 2018 was 7094.
- Number of samples received from major hospitals participated in the Program till December 2018 is illustrated in (figure 6).
- Total Number of cases discovered since the establishment of the NBS Program from August 2005 till December 2018 was 1046 See (figure 7).
- The following Manuscript was published,
- The Prevalence of Phenylketonuria in Arab Countries, Turkey, and Iran: A Systematic Review. El-Metwally A, Yousef Al-Ahaidib L, Ayman Sunqurah A, Al-Surimi K, Househ M, Alshehri A, Da'ar OB, Abdul Razzak H, AlOdaib AN. Biomed Res Int. 2018 Apr 18; 2018. PMID: 29850564.

Future Directions

One of the country's 2030 visions is to achieve the "Vibrant Society with Strong Foundations" theme that aims to offer a fulfilling & healthy life through improving healthcare service by ease of access to healthcare services and strengthen prevention against health threats. Accordingly, future efforts will be continued to attain this aim through the following:

1. Preparations of a comprehensive newborn screening guideline to unify and enhance the quality of the newborn screening laboratory and improve the provision of its diagnostic services. Expanding screening accessibility and coverage of countries newborns through enrollment of more clients from private & university hospitals.

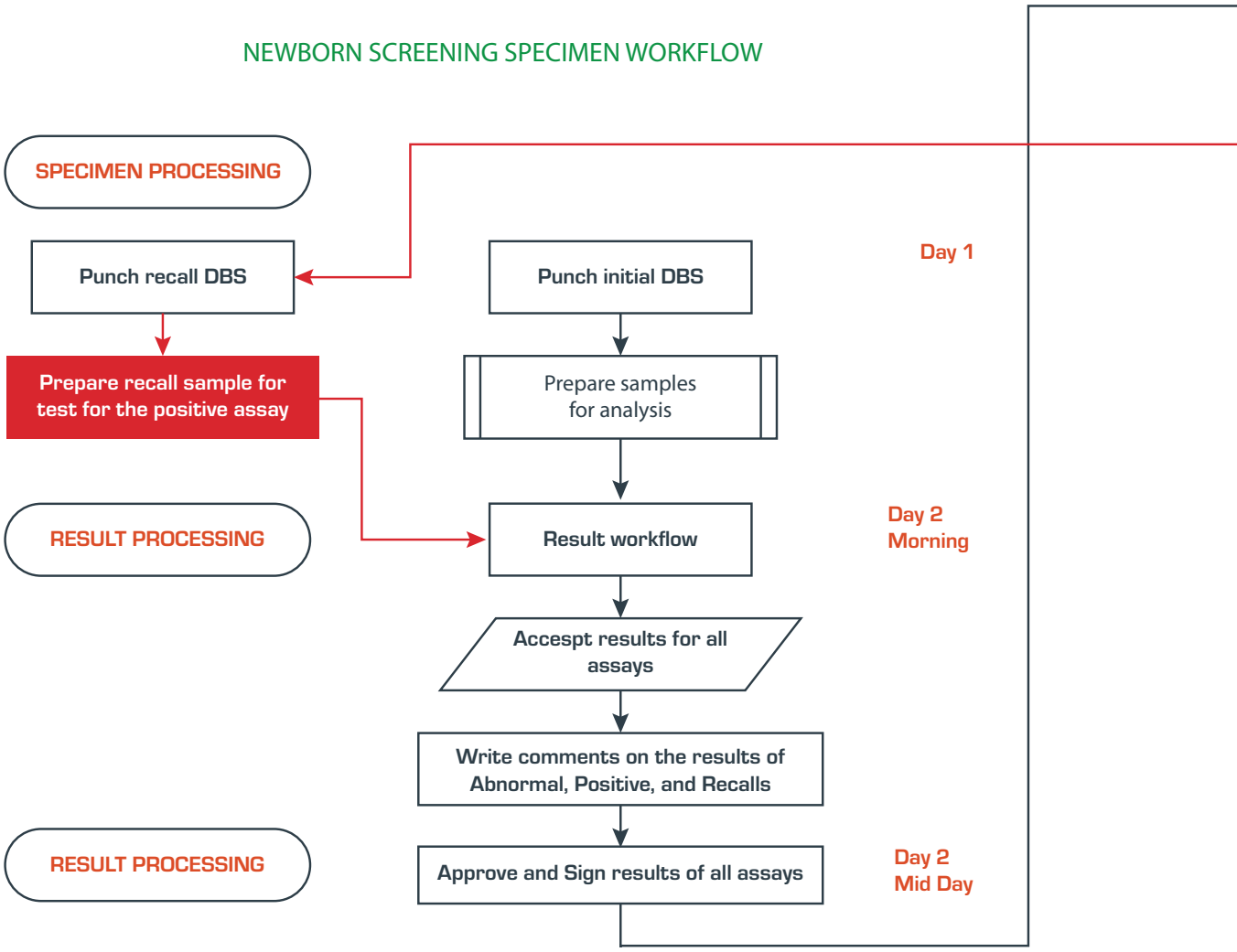
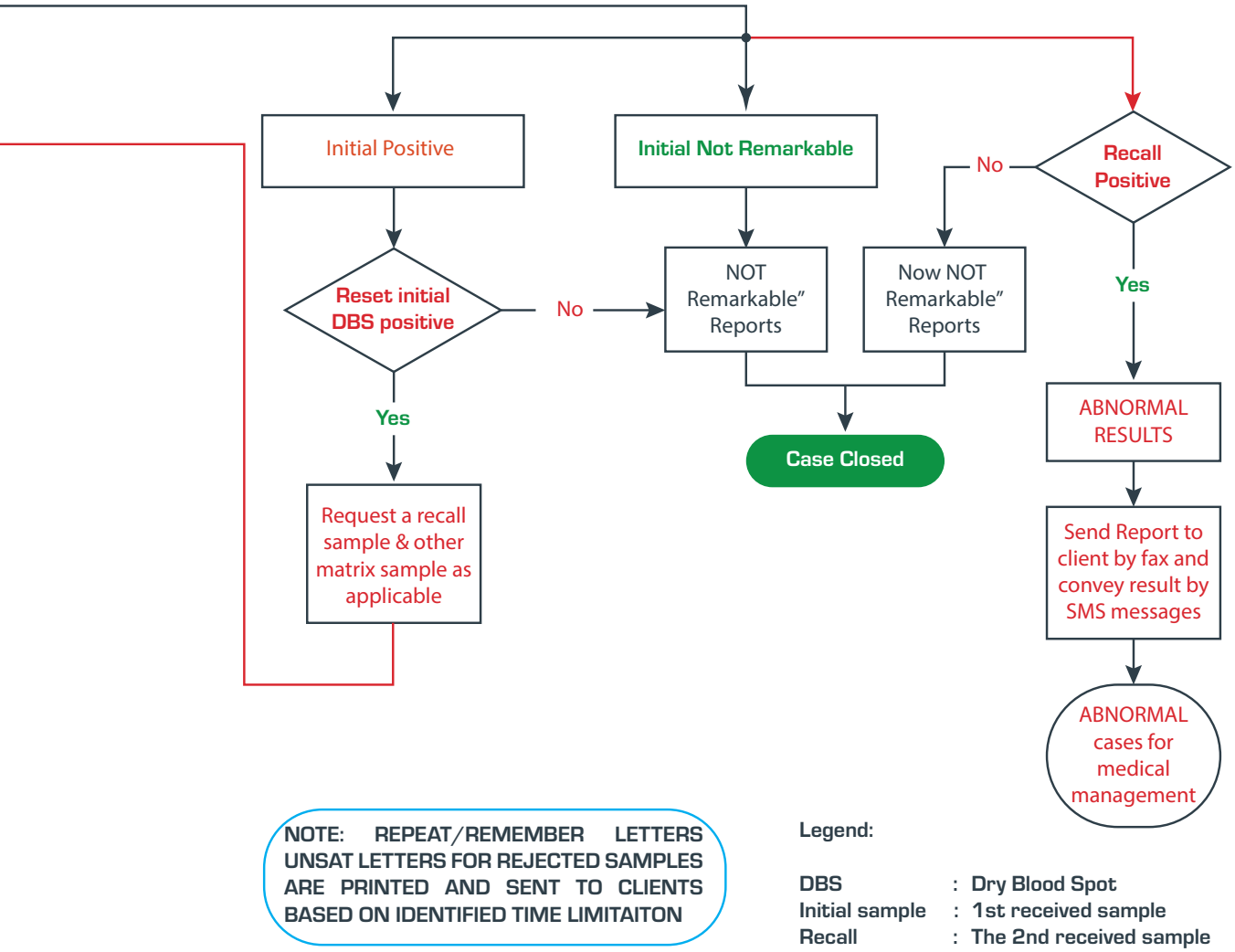


Figure 1: The newborn screening workflow.

2. Preparation towered establishment of a unified registry platform for disorders included in the newborn screening program.
3. Conducting more of population data research in addition to metabolomics research that eventually will assess in evaluating and enhancing the effectiveness of the screening process.



NOTE: REPEAT/REMEMBER LETTERS UNSAT LETTERS FOR REJECTED SAMPLES ARE PRINTED AND SENT TO CLIENTS BASED ON IDENTIFIED TIME LIMITAITON

Legend:

DBS : Dry Blood Spot
Initial sample : 1st received sample
Recall : The 2nd received sample

Disorders Included in the Program
(Phenylketonuria (PKU
(Maple Syrup Urine Disease (MSUD
(Argininosuccinate Lyase deficiency (ASL
(Citrullinemia (CIT
(Propionic Acidemia (PPA
(Methylmalonic Acidemia (MMA
(Glutaric Acidemia type-I (GA-I
(Isovaleric Acidemia (IVA
.(MCC 3) Methylcrotonyl-CoA Carboxylase Deficiency-3
(Medium-Chain Acyl-CoA Dehydrogenase Deficiency (MCAD
(Very Long-Chain Acyl-CoA Dehydrogease Deficiency (VLCAD*
(Methylglutaryl-CoA Lyase Deficiency (HMG-3-Hydroxy-3
(Beta-Ketothiolase Deficiency (BKT
(Biotinidase Deficiency (BTD
(Galactosemia (GALT
(Congenital Hypothyroidism (CH
(Congenital Adrenal Hyperplasia (CAH

Table 1: Disorders included in the Newborn Screening Panel

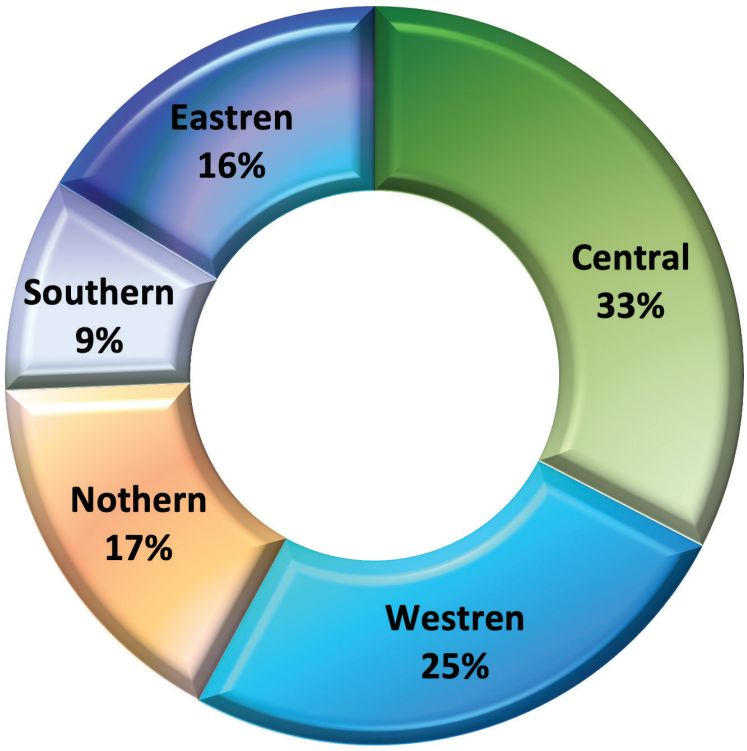


Figure 2: Regional distributions of NBS samples received during 2018

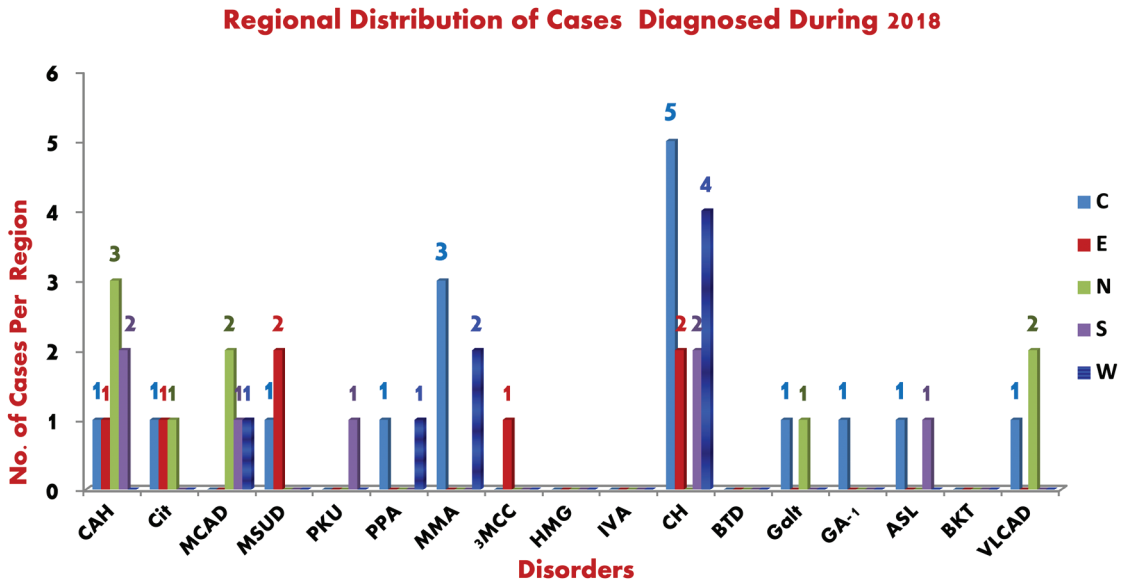


Figure 3A: Demonstrates regional distribution of each disorder during 2018

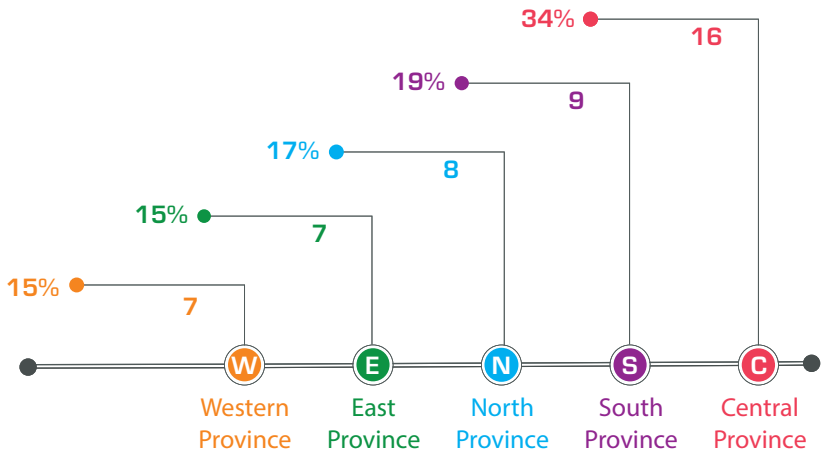


Figure 3B: Shows the total number of detected cases per regions during 2018.

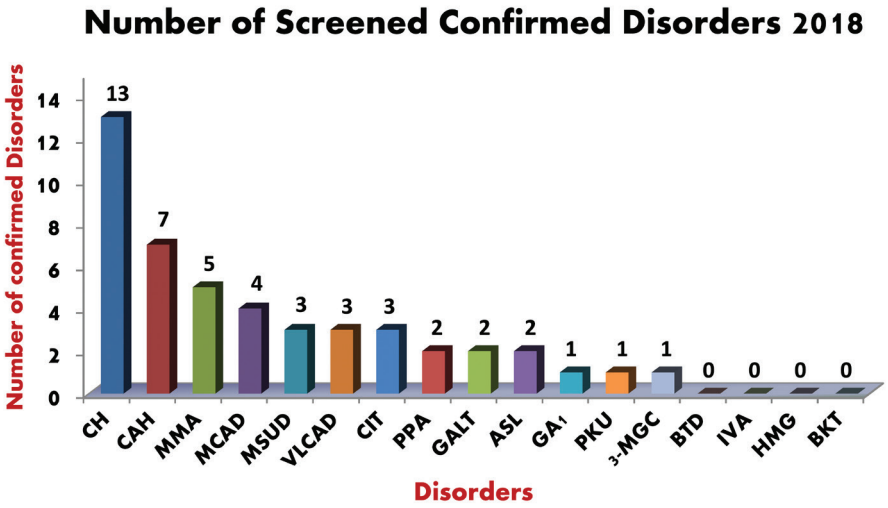


Figure 4: Showing the number of disorders detected during 2018

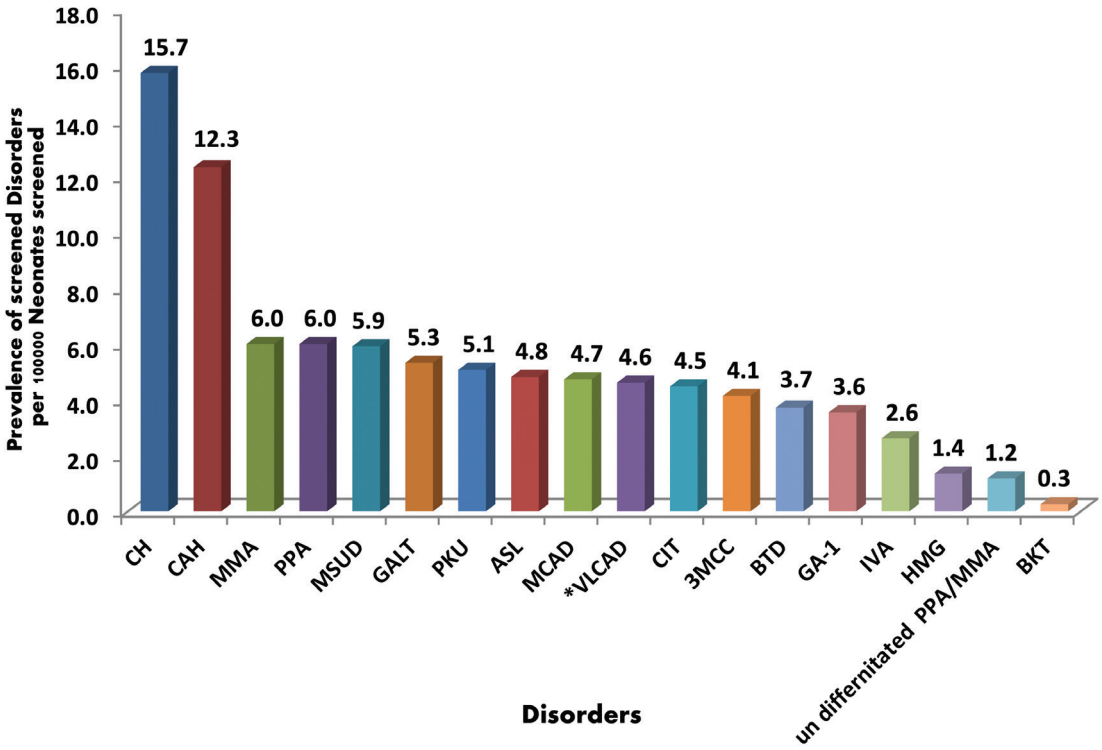


Figure 5: Demonstrating the accumulative prevalence of each disorder per the total number of newborns screened during the period August 2005- December 2018 which is 1182468 newborns.

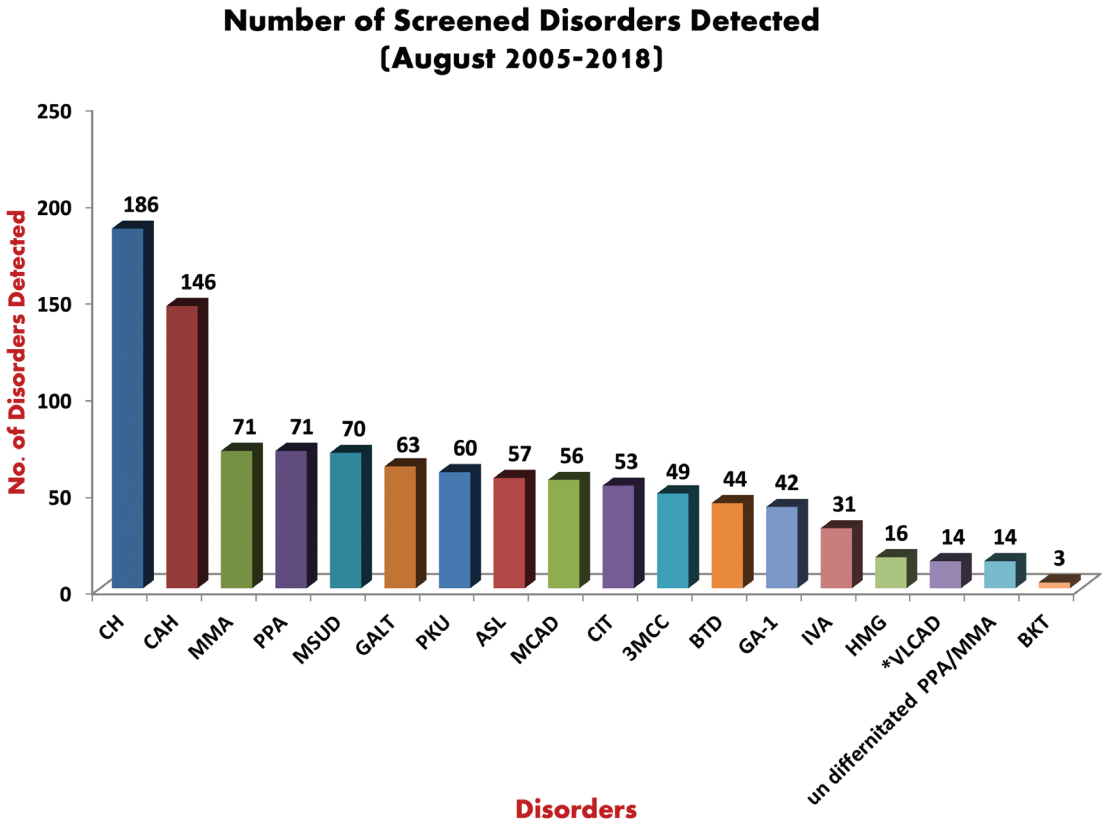


Figure 7: Shows the number of disorders detected since the beginning of the NBS Program (August 2005- December 2018).

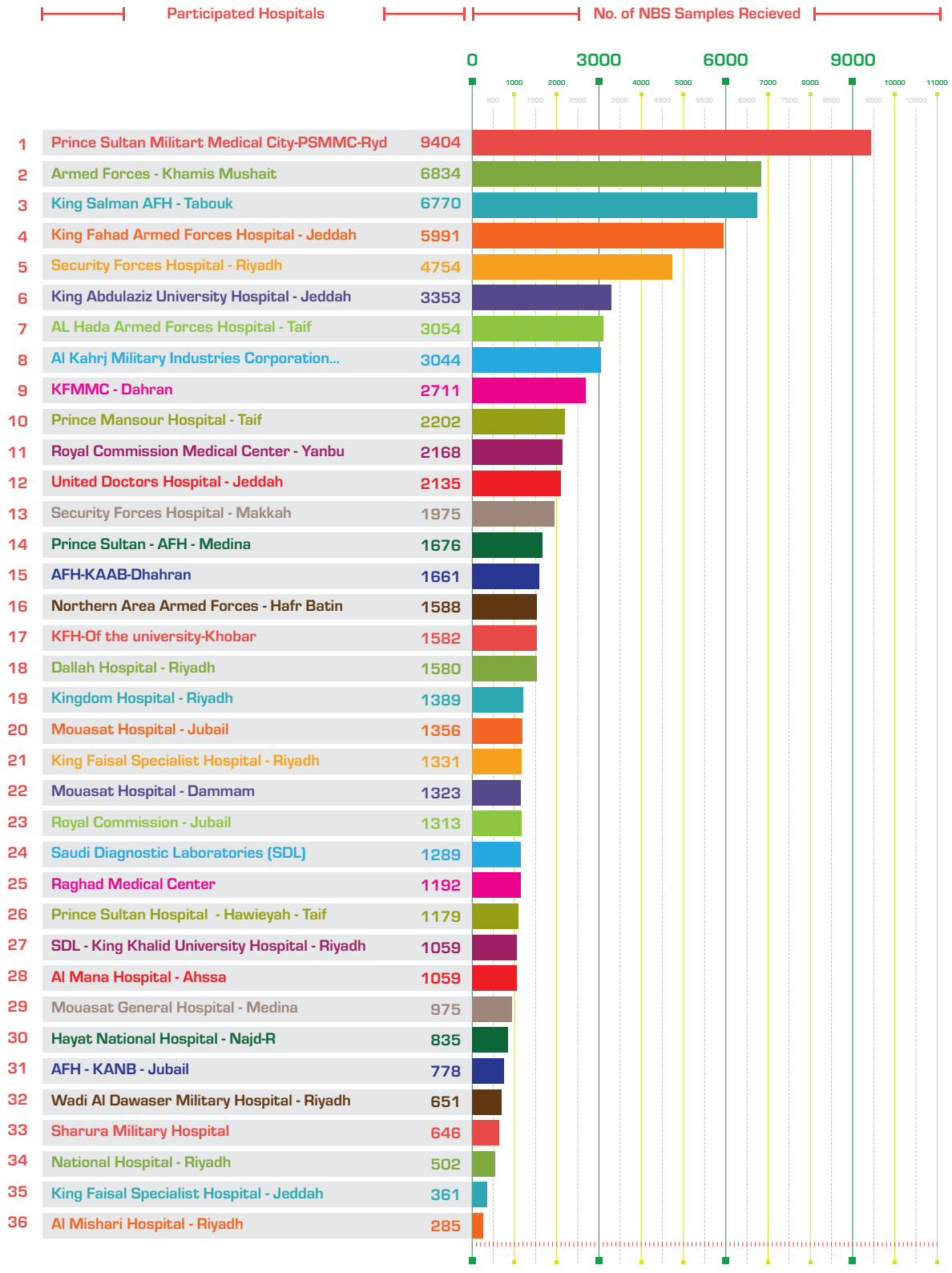


Figure 6: Demonstrating the number of newborn samples received from major participated hospitals during 2018

The Framework of Reference to Access the General Curriculum for Students with Disabilities in GCC

Background and objectives of the project

The aim of this frame is to support the access of students with disabilities to the general curriculum in their educational institutions as an alternative to the special curriculum by clarifying the concept and nature of the general curriculum for teachers of general education and special education, so as to help them to understand the dimensions of this curriculum, its elements and types, and the importance of their access to the curriculum General. It aims to provide these teachers with a deep understanding of the nature of access to the general curriculum of these students and the mechanisms by which such access can be supported. In addition to explaining how these students benefit from the general curriculum in a way that corresponds to the abilities of each student. Help them in how to plan the access of the general curriculum in a way that ensures that students with disabilities learn without underestimating their ability and in a deeper way to integrate them.

Final completion of the second part of the project (Practical and Scientific guide preparation)

- Working in a team to prepare the practical and scientific section of the whole frame in each dialog and design and remove it in its final form.
- Preparation and design of the "Trainer's Manual" for the frame, which contains instructions and procedures for training and its mechanism.
- Prepare and Design "Trainee Manual" which includes activities to be offered to trainees to ensure that they are familiar with the content provided to them.
- Design and output of the application frame, which contains all the activities found in the trainee's guide.
- The training program was offered in:
  - ◊ Kingdom of Bahrain on 26-27/4/2018 in cooperation with the Ministry of Education of the Kingdom of Bahrain.
  - ◊ Kuwait on 26-27/9/2018 in cooperation with the Ministry of Education in Kuwait.
  - ◊ Kingdom of Saudi Arabia on 3-4/10/2018 in cooperation with the National Center for Vocational Education in the Ministry of Education.
  - ◊ United Arab Emirates on 4-5/11/2018 in cooperation with the Ministry of Education at the Teacher Training Institute in Ajman.
  - ◊ Sultanate of Oman on 5-6 / 12/2018 in cooperation with the Ministry of Education in Muscat.

After the completion of the training program, a comprehensive review of all the evaluations issued by the training programs provided and the development of the final additions to the bag was done, where:

- Taking all the visuals from the training programs established in the Kingdom of Bahrain, Kuwait, the Kingdom of Saudi Arabia, the United Arab Emirates and the Sultanate of Oman and adding the contents and axes based on the proposals received.
- A final review of all the contents of the frame has been made to ensure that any design and output errors are free.
- The portfolio is finalized and its contents (Trainer's Guide and Trainee's Guide) delivered to King Salman Center and the Education office.
- His Royal Highness the Chairman of the Board of Trustees inaugurated the terms of reference for students with disabilities to the general curriculum in the presence of the Minister of Education and members of the Board of Trustees.
- Design of paper copies as well as digital copies to be published after approval for publication by King Fahd National Library.
- It will be uploaded on the center's website in preparation for its publication to all sectors and destinations.
- A plan of action will be developed for all regions of the kingdom to provide the frame through a group of trainers from different regions of the kingdom after being trained in the center.
- The project was completed by the end of December 2018.

The terms of reference for pupils with disabilities have been issued to the general curriculum

This release is the result of the distinctive partnership between the King Salman Center for Disability Research and the Arab Bureau of Education for the Gulf States, which aims to provide

the necessary support for students with disabilities, to reach the general curriculum in the comprehensive school and the less restrictive environments and to give these students skills Academic, social and integration with their regular peers. This frame seeks to support the efforts of the Member States of the Arab Bureau of Education for the Gulf States in achieving equal opportunities for all students.

The frame of reference is divided into four publications (registered in the King Fahd Library):

- Theoretical and theological aspects (Deposit No. 10421/1439 ISBN 5-427-15-9960)
- And the practical and scientific side (deposit No. 10424/1439 ISBN-727-15-9960- x)
- Trainer's Manual (ISBN 10423/1439 1-726-15-9960)
- Trainee's Manual (ISBN 10422/1439 3-725-15-9960)

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