مركز الملك سلمان لأبحاث الإعاقة
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]

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.

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Scientific Reports

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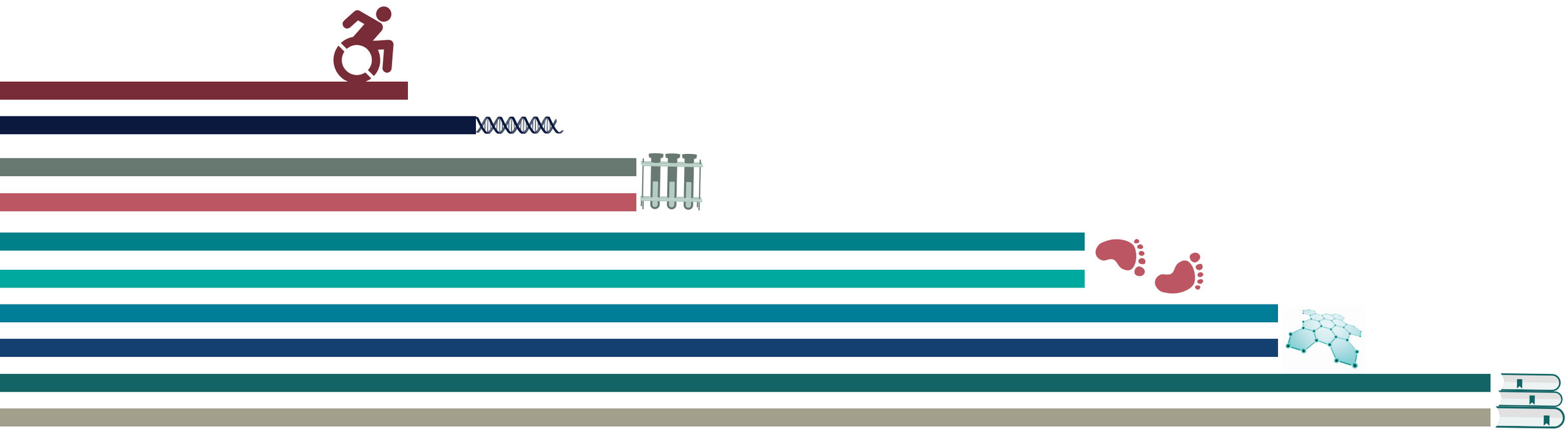


A novel ISLR-2linked autosomal recessive syndrome of congenital hydrocephalus, arthrogryposis and abdominal distension

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.

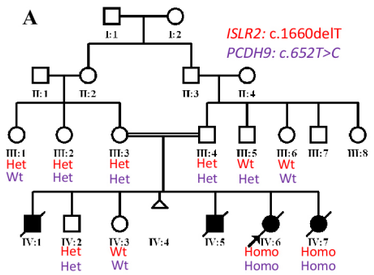


Figure (A) Pedigree of the family and their genotypes for both variants in ISLR2 and PCDH9.

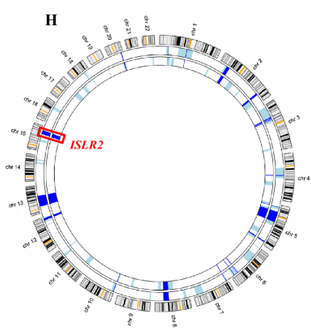


Figure (H) Circular ideogram of the available affected members' genome.

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.

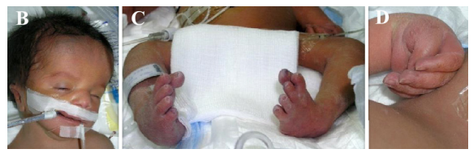


Figure (B-D) Clinical images of the index.

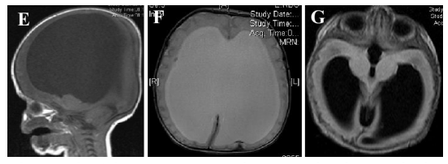


Figure (E-G) MRI images showing hydrocephalus.

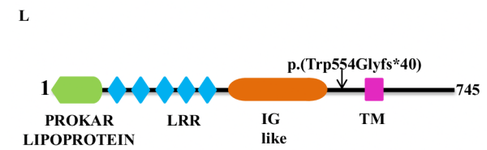


Figure (L) ISLR2 protein structure showing the mutation and functional domains.

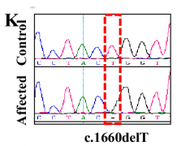


Figure (K) Sequence chromatogram showing deletion of T.

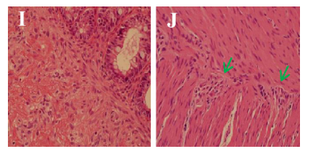
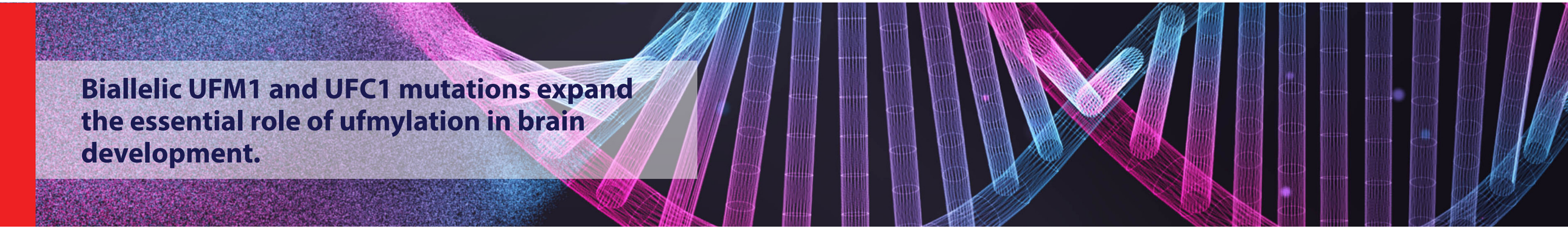


Figure (I-J) Rectal biopsy.



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.

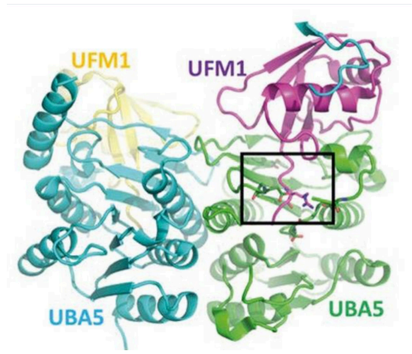
The main finding of this project includes:

- 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.

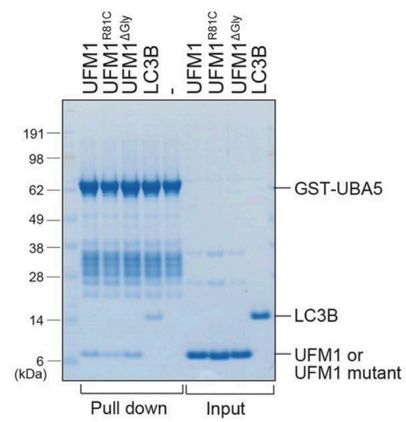
Conclusion & Future Directions:

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.

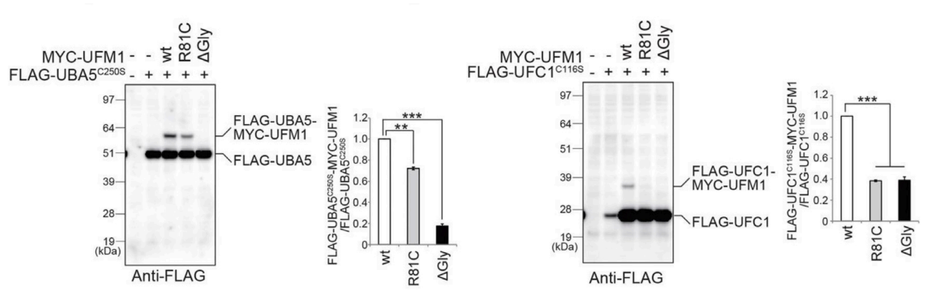
Hypomorphic effect of the UFM1 mutation on the UFM system



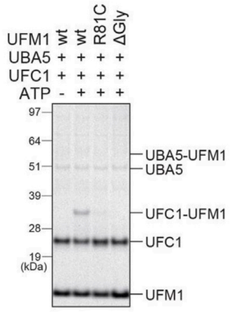
Molecular basis for the effect of the UFM1R81C mutation.



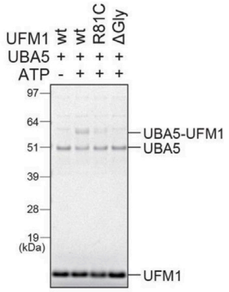
In vitro pull-down assay. Pull-down assay with GST-UBA5 and UFM1, UFM1 mutants or LC3B.



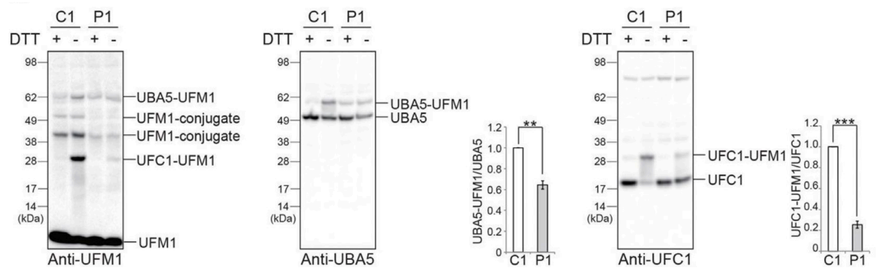
Immunoblot assay.



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.

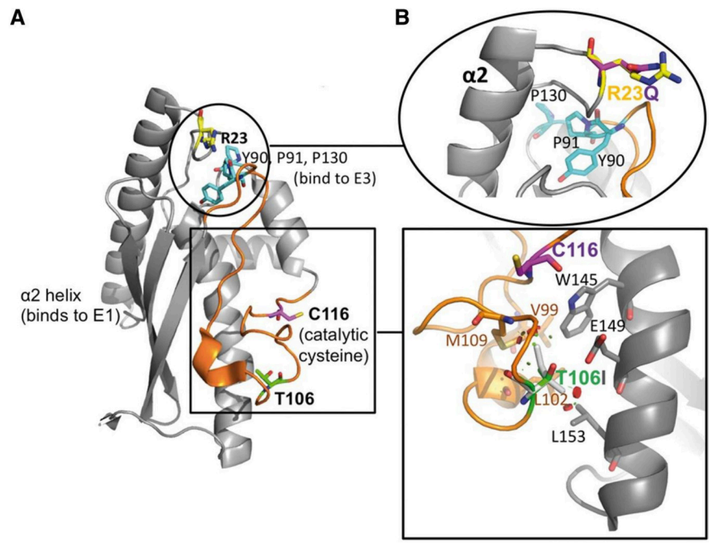


Figure (A) Localization of the key binding sites on UFC1. Binding sites for E1 and E3 are indicated. **Figure (B)** Bottom: Magnification of Thr106.

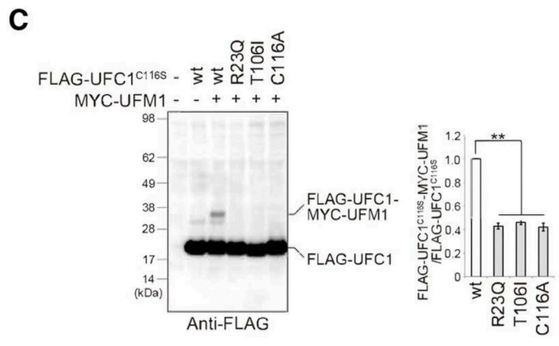


Figure (C) Immunoblot assay.

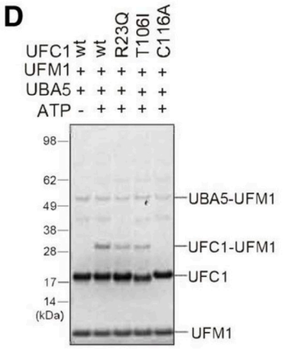


Figure (D) In vitro thioester formation assay of UFM1 by UFC1.

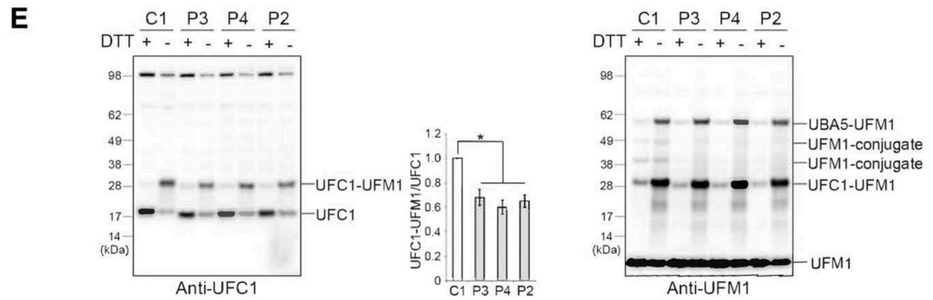
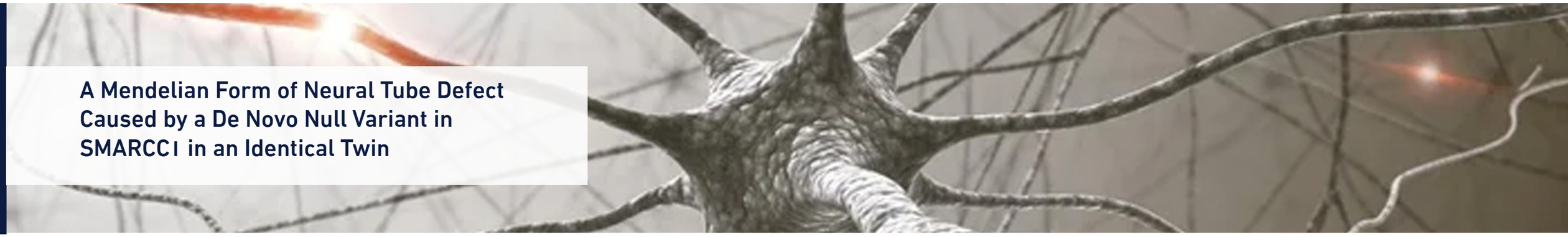


Figure (E) Immunoblot analysis in case (P2, P3, P4: V:1) and control (C1: a healthy Sudanese young females) lymphoblasts.

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.

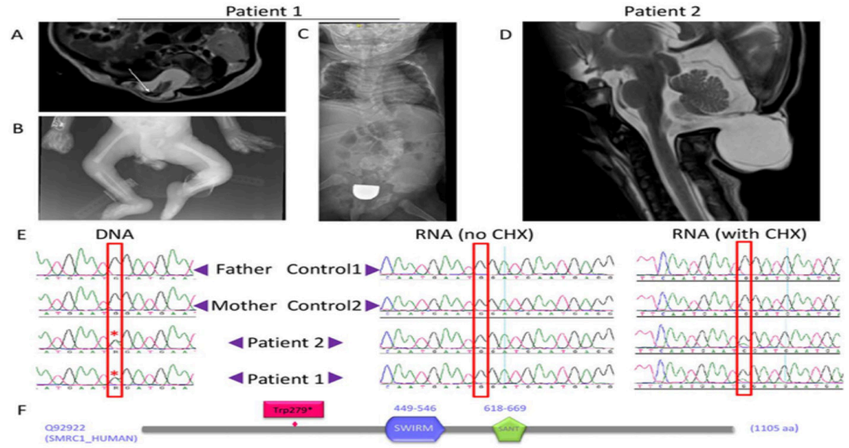


Figure: NTD phenotype observed in a monozygotic twin with a de novo, likely null, allele in SMARC1A. (A) T2-WI image of the index. **(B)** Right talipes calcaneovalgus deformity and left club foot seen in the index. **(C)** Left convex congenital lumber scoliosis secondary to abnormal segmentation. **(D)** 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

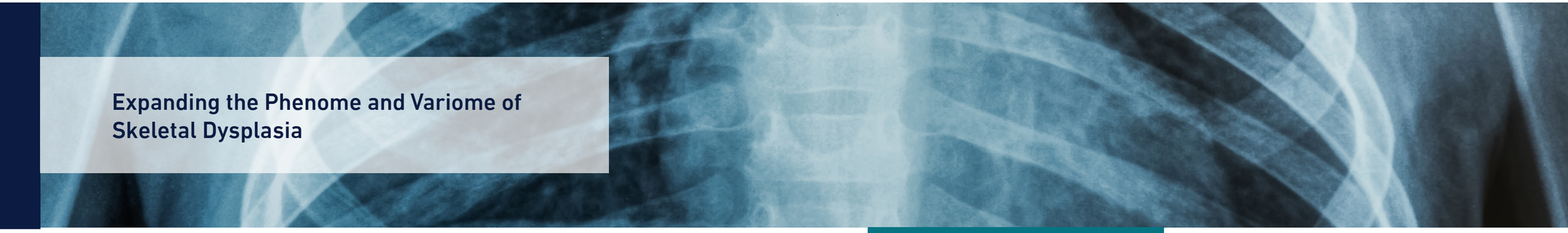
3.8%

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

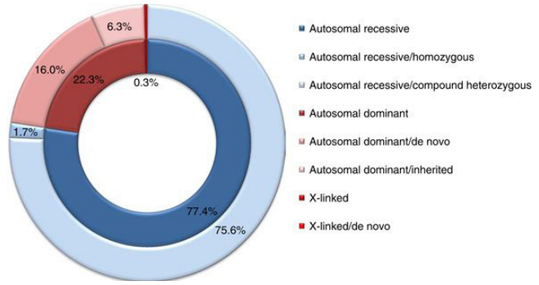


Figure: Doughnut chart showing the proportion of autosomal recessive (homozygous and compound heterozygous shown separately), dominant, and X-linked (inherited and de novo shown separately) conditions in the study cohort.

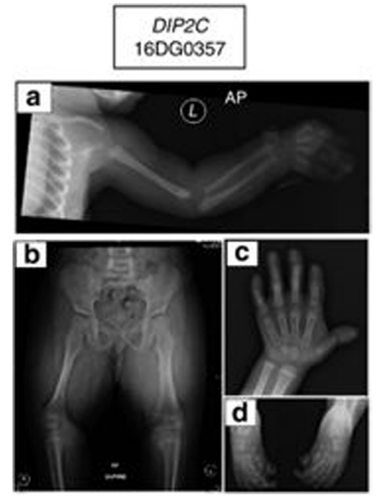


Figure (A–B): A patient with a mutation in DIP2C, **(C)** clinodactyly with shortening of metacarpal bones, **(D)** bilateral metatarsus adduction, bilateral shortening of 1st metatarsals

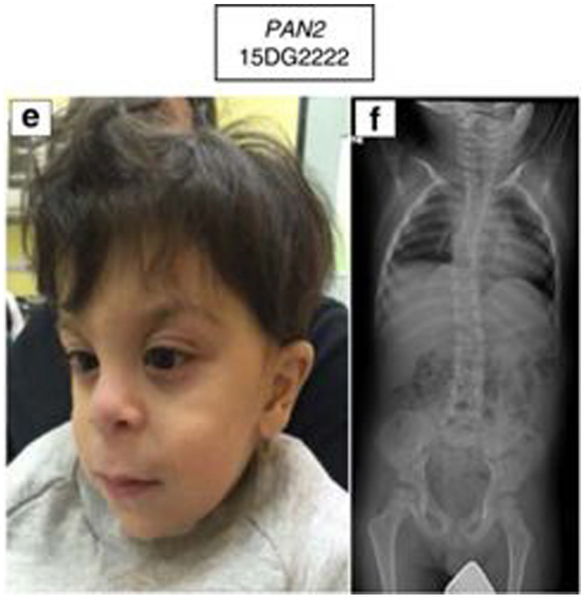


Figure (E and F) A patient with a mutation in PAN2showing plagiocephaly

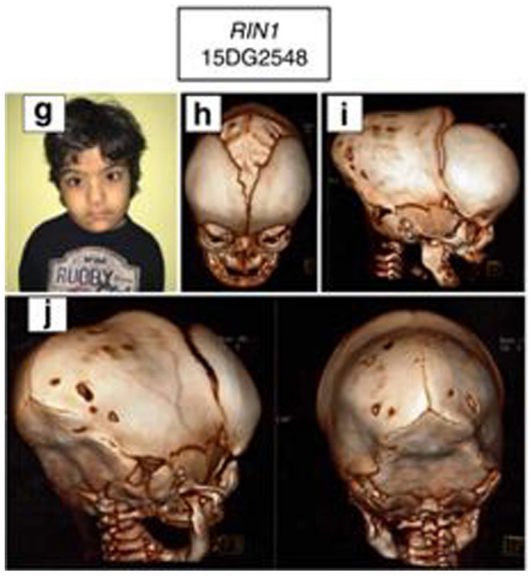


Figure (G and J) A patient with a mutation in RIN1 showing plagiocephaly

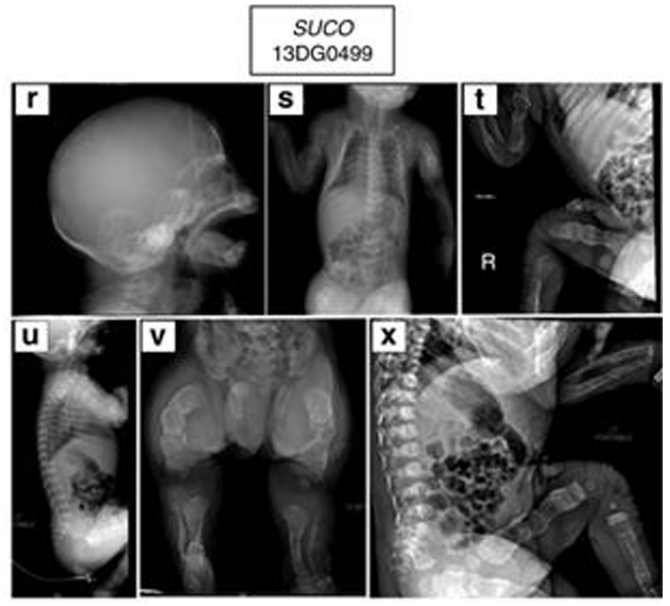


Figure (K–Q) A patient with a mutation in WNT3A

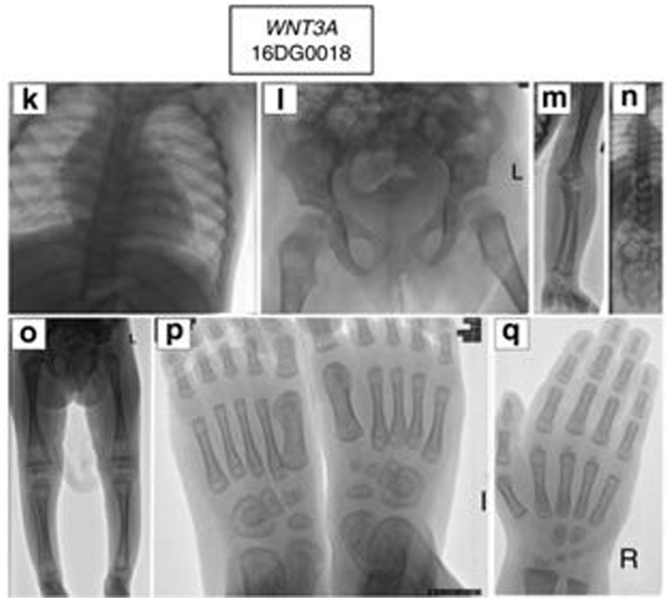


Figure (R–X) A patient with a mutation in SUCO

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